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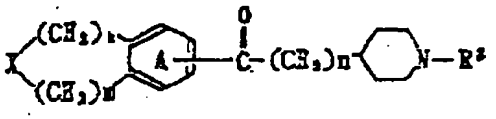
(54) Condensed heterocyclic compounds, their production and use.

(57) A condensed heterocyclic derivative of the formula (I):



(I)

wherein X is an oxygen atom, a sulfuir atom or R^1-N< wherein R^1 is a hydrogen atom, a hydrocarbon group which may be substituted or an acyl group which may be substituted; R^2 is a hydrogen atom or a hydrocarbon group which may be substituted; ring A is a benzene ring which may be substituted, k is a whole number of 0 to 3; m is a whole number of 1 to 8; and n is a whole number of 1 to 6, or a salt thereof exhibiting high colinesterase inhibitory activity, and a method for producing the same.

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The present invention relates to novel condensed heterocyclic compounds or their salts. The compounds of the invention are useful as a medicine and a cholinesterase inhibitor and specifically as a therapeutic and/or prophylactic agent for senile dementia, Alzheimer's disease and so on.

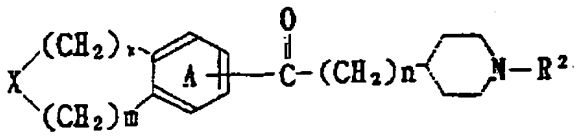
In these days of aging society, there has been proposed a variety of compounds which have therapeutic and prophylactic efficacy for senile dementia. It has been found that physostigmine, a naturally-occurring cholinesterase inhibitor, has therapeutic and/or prophylactic activity for senile dementia. However, physostigmine has the drawbacks of a short duration of action, high toxicity and so on.

Meanwhile, as synthetic drugs for a colinesterase inhibitor, depressant or so, a variety of heterocyclic compounds have been proposed (e.g. USP 4,064,255, USP 4,208,417, USP 4,849,431, USP 4,895,841, Japanese Publish unexamined patent application No. 169569/1990 and EP-A-0,378,207).

However, what is needed now is a compound which is more active, longer-acting and less toxic than the compounds already known to have therapeutic and/or prophylactic efficacy for senile dementia.

The present invention provides a novel class of compounds which is useful as a cholinesterase inhibitor and particularly as a therapeutic and/or prophylactic agent for senile dementia, Alzheimer's disease and so on.

The inventors of present invention explored compounds which could be of use as medicament for improving the functions of the the central nervous system and particularly compounds of value for the relief of senile dementia, Alzheimer's disease and so on due to brain ischemia and succeeded in the creation of a condensed heterocyclic compound of the formula (I):

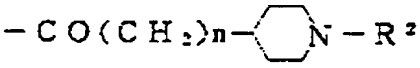


(I)

wherein X is an oxygen atom, a sulfur atom or R^1-N< wherein R^1 is a hydrogen atom, a hydrocarbon group which may be substituted or an acyl group which may be substituted;

R^2 is a hydrogen atom or a hydrocarbon group which may be substituted; ring A is a benzene ring which may be substituted; k is a whole number of 0 to 3; m is a whole number of 1 to 8; and n is a whole number of 1 to 6, or a salt thereof.

The compound (I) or its salt according to the present invention is structurally characterized in that the hetero atom (O,S or N)-containing heterocycle fused to the benzene ring is a saturated ring and that a substituent group of the formula:



is bound directly to a carbon atom of the benzene ring. This compound is believed to be a novel compound which has not been disclosed in the literature.

Referring to the above formula (I), the "hydrocarbon group" of "the hydrocarbon group which may be substituted" as designated by R^1 and R^2 includes acyclic, cyclic, saturated, unsaturated or their optionally combinated hydrocarbon groups.

The acyclic saturated hydrocarbon group includes straight-chain or branched C_{1-11} alkyl groups (e.g. methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, tert-butyl, n-pentyl, n-hexyl).

The acyclic unsaturated hydrocarbon group includes straight-chain or branched C_{2-4} alkenyl groups (e.g. vinyl, allyl, 2-butenyl) and C_{2-4} alkynyl groups (e.g. propargyl, 2-butynyl).

The cyclic saturated hydrocarbon group includes C_{3-7} monocyclic cycloalkyl groups (e.g. cyclobutyl, cyclopentyl, cyclohexyl) and C_{8-14} bridged cyclic saturated hydrocarbon groups (e.g. bicyclo[3.2.1]oct-2-yl, bicyclo[3.3.1]non-2-yl, adamantan-1-yl).

The cyclic unsaturated hydrocarbon group includes phenyl, naphthyl and so on.

The "hydrocarbon group" of the "hydrocarbon group which may be substituted" as designated by R^1 and R^2 may be an optionally combined hydrocarbon group representing an optional combination of the above-mentioned acyclic, cyclic, saturated and unsaturated hydrocarbon groups, such as C_{7-18} aralkyl (such as phenyl C_{1-12} alkyl and naphthyl C_{1-8} alkyl, e.g. phenylmethyl, phenylethyl, phenylpropyl, phenylbutyl, phenylpentyl, phenylhexyl, α-naphthylmethyl), C_{8-18} arylalkenyl (such as aryl C_{2-12} alkenyl,

e.g. styryl, cinnamyl, 4-phenyl-2-butenyl, 4-phenyl-3-butenyl), C_{8-18} arylalkynyl (such as aryl C_{2-12} alkynyl, e.g. phenylethynyl, 3-phenyl-2-propynyl, 3-phenyl-propynyl), C_{3-7} cycloalkyl-C_{1-5} alkyl (e.g. cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, cycloheptylmethyl, cyclopropylethyl, cyclobutylethyl, cyclopentylethyl, cyclohexylethyl, cycloheptylethyl, cyclopropylbutyl, cyclobutylbutyl, cyclopentylbutyl, cyclohexylbutyl, cycloheptylbutyl, cyclopropylpentyl, cyclobutylpentyl, cyclopentylpentyl, cyclohexylpentyl, cycloheptylpentyl, cyclopropylhexyl, cyclobutylhexyl, cyclopentylhexyl, cyclohexylhexyl, cycloheptylhexyl) groups and so on.

The preferable examples of the "hydrocarbon group" of the "hydrocarbon group which may be substituted" as designated by R^1 include a straight-chain or branched C_{1-7} alkyl group (e.g. methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, tert-butyl, n-pentyl, n-hexyl) or a C_{7-10} aralkyl group (e.g. phenylmethyl, phenylethyl, phenylpropyl) and the examples of the "hydrocarbon group" of the "hydrocarbon group which may be substituted" as designated by R^2 include a C_{7-10} aralkyl (e.g. phenylmethyl, phenylethyl, phenylpropyl).

The acyclic saturated, acyclic unsaturated and cyclic saturated hydrocarbon groups mentioned above for R^1 and R^2 may be substituted by 1 to 5 substituents selected from the group consisting of halogen (e.g. fluoro, chloro, bromo, iodo), nitro, cyano, hydroxy, C_{1-4} alkoxy (e.g. methoxy, ethoxy, propyloxy, butyloxy, isopropyloxy), C_{1-4} alkylthio (e.g. methylthio, ethylthio, propylthio), amino, mono- or di-C_{1-4} alkyl-substituted amino (e.g. methylamino, ethylamino, propylamino, dimethylamino, diethylamino), cyclic amino (e.g. pyrrolidino, piperidino, morpholino), C_{1-4} alkylcarbonylamino (e.g. acetylamino, propionylamino, butyrylamino), C_{1-4} alkylsulfonylamino (e.g. methylsulfonylamino, ethylsulfonylamino), C_{1-4} alkoxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl), hydroxycarbonyl, C_{1-6} alkylcarbonyl (e.g. methylcarbonyl, ethylcarbonyl, propylcarbonyl), carbamoyl, mono- or di-C_{1-4} alkyl-substituted carbamoyl (e.g. methylcarbamoyl, ethylcarbamoyl), C_{1-6} alkylsulfonyl (e.g. methylsufonyl, ethylsulfonyl, propylsulfonyl) and so on.

The substituents on the "benzene ring which may be substituted" as designated by ring A in formula (I) and the substituents on the cyclic unsaturated hydrocarbon group as designated by R^1 and R^2 include C_{1-4} alkyl (e.g. methyl, ethyl, propyl, butyl), halogen (e.g. fluoro, chloro, bromo, iodo), nitro, cyano, hydroxy, C_{1-4} alkoxy (e.g. methoxy, ethoxy, propyloxy, butyloxy, isopropyloxy), C_{1-4} alkylthio (e.g. methylthio, ethylthio, propylthio, isopropylthio, butylthio), amino, mono- or di-C_{1-4} alkyl-substituted amino (e.g. methylamino, ethylamino, propylamino, dimethylamino, diethylamino), cyclic amino (e.g. pyrrolidino, piperidino, morpholino), C_{1-4} alkylcarbonylamino (e.g. acetylamino, propionylamino, butyrylamino), aminocarbonyloxy, mono- or di-C_{1-4} alkyl-substituted aminocarbonyloxy (e.g. methylaminocarbonyloxy, ethylaminocarbonyloxy, dimethylaminocarbonyloxy, diethylaminocarbonyloxy), C_{1-4} alkylsufonylamino (e.g. methylsulfonylamino, ethylsulfonylamino, propylsulfonylamino), C_{1-4} alkoxycarbonyl (e.g. metoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isobutoxycarbonyl), hydroxycarbonyl, C_{1-6} alkylcarbonyl (e.g. methylcarbonyl, ethylcarbonyl, butylcarbonyl), C_{3-6} cycloalkylcarbonyl (e.g. cyclohexylcarbonyl), carbamoyl, mono- or di-C_{1-4} alkyl-substituted carbamoyl (e.g. methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, butylcarbamoyl, diethylcarbamoyl, dibutylcarbamoyl) and C_{1-6} alkylsulfonyl (e.g. methylsulfonyl, ethylsulfonyl, propylsulfonyl) and C_{3-6} cycloalkylsulfonyl (e.g. cyclopentylsulfonyl, cyclohexylsulfonyl) as well as a phenyl naphthyl, phenoxy, benzoyl, phenoxycarbonyl, phenyl-C_{1-4} alkylcarbamoyl (e.g. phenylmethylcarbamoyl, phenylethylcarbamoyl, phenylpropylcarbamoyl), phenylcarbamoyl, phenyl-C_{1-4} alkylcarbonylamino (e.g. phenylmethylcarbonylamino, phenylethylcarbonylamino), benzoylamino, phenyl-C_{1-4} alkylsulfonyl (e.g. phenylmethylsulfonyl, phenylethylsulfonyl), phenylsulfonyl, phenyl-C_{1-4} alkylsulfinyl (e.g. phenylmethylsulfinyl, phenylethylsulfinyl), phenyl-C_{1-4} alkylsulfonylamino (e.g. phenylmethylsulfonylamino, phenylethylsulfonylamino) or phenylsulfonylamino which may have 1 to 4 substituents, for example selected from the group consisting of C_{1-4} alkyl groups such as methyl, ethyl, propyl, butyl, isopropyl, etc., C_{1-4} alkoxy groups such as methoxy, ethoxy, n-propyloxy, i-propyloxy, n-butyloxy, etc., halogen such as chloro, bromo and iodo, hydroxy, benzyloxy, amino, mono- or di-C_{1-4} alkyl-substituted amino such as mentioned above, nitro, and C_{1-6} alkylcarbonyl such as mentioned above and so on. The appropriate number of such substituents on the benzene ring or cyclic unsaturated hydrocarbon group is 1 to 3.

The optionally combined hydrocarbon group as designated by R^1 and R^2 may be substituted by 1 to 5 substituents selected from the group consisting of C_{1-4} alkyl (e.g. methyl, ethyl, propyl, butyl), halogen (e.g. fluoro, chloro, bromo, iodo), nitro, cyano, hydroxy, C_{1-4} alkoxy (e.g. methoxy, ethoxy, propyloxy, butyloxy, isopropyloxy), C_{1-4} alkylthio (e.g. methylthio, ethylthio, propylthio, isopropylthio, butylthio), amino, mono- or di-C_{1-4} alkyl-substituted amino (e.g. methylamino, ethylamino, propylamino, dimethylamino, diethylamino), cyclic amino (e.g. pyrrolidino, piperidino, morpholino), C_{1-4} alkylcarbonylamino (e.g. acetylamino, propionylamino, butyrylamino), aminocarbonyloxy, mono- or di-C_{1-4} alkyl-substituted aminocarbonyloxy (e.g. methylaminocarbonyloxy, ethylaminocarbonyloxy, dimethylaminocarbonyloxy,

diethylaminocarbonyloxy), C_{1-4} alkylsufonylamino (e.g. methylsulfonylamino, ethylsulfonylamino, propylsulfonylamino), C_{1-4} alkoxycarbonyl (e.g. metoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isobutoxycarbonyl), hydroxycarbonyl, C_{1-6} alkylcarbonyl (e.g. methylcarbonyl, ethylcarbonyl, butylcarbonyl), C_{3-6} cycloalkylcarbonyl (e.g. cyclohexylcarbonyl), carbamoyl, mono- or di-C_{1-4} alkyl-substituted carbamoyl (e.g. methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, butylcarbamoyl, diethylcarbamoyl, dibutylcarbamoyl), C_{1-6} alkylsulfonyl (e.g. methylsulfonyl, ethylsulfonyl, propylsulfonyl) and C_{3-6} cycloalkylsulfonyl (e.g. cyclopentylsulfonyl, cyclohexylsulfonyl) as well as a phenyl, naphthyl, phenoxy, benzoyl, phenoxycarbonyl, phenyl-C_{1-4} alkylcarbamoyl (e.g. phenylmethylcarbamoyl, phenylethylcarbamoyl, phenylpropylcarbamoyl), phenylcarbamoyl, phenyl-C_{1-4} alkylcarbonylamino (e.g. phenylmethylcarbonylamino, phenylethylcarbonylamino), benzoylamino, phenyl-C_{1-4} alkylsulfonyl (e.g. phenylmethylsulfonyl, phenylethylsulfonyl), phenylsulfonyl, phenyl-C_{1-4} alkylsulfinyl (e.g. phenylmethylsulfinyl, phenylethylsulfinyl), phenyl-C_{1-4} alkylsulfonylamino (e.g. phenylmethylsulfonylamino, phenylethylsulfonylamino) or phenylsulfonylamino which may have 1 to 4 substituents, for example selected from the group consisting of C_{1-4} alkyl groups such as methyl, ethyl, propyl, butyl, isopropyl, etc., C_{1-4} alkoxy groups such as methoxy, ethoxy, n-propyloxy, i-propyloxy, n-butyloxy, etc., halogen such as chloro, bromo and iodo, hydroxy, benzyloxy, amino, mono- or di-C_{1-4} alkyl-substituted amino such as mentioned above, nitro, and C_{1-6} alkylcarbonyl such as mentioned above and so on.

The "acyl" of the "acyl group which may be substituted" as designated by R^1 includes carboxylic acid acyl groups (e.g. hormyl, C_{2-8} alkyl- or phenylcarbonyl groups such as acetyl, propionyl, butyryl, benzoyl, etc.), sulfonic acid acyl groups (e.g. C_{1-7} alkyl- or phenylsulfonyl groups such as methanesulfonyl, benzenesulfonyl, p-toluensulfonyl, etc.), phosphonic acid acyl groups (e.g. C_{1-7} alkyl- or phenylphosphonyl groups such as methanephosphonyl, benzenephosphonyl, etc.), and substituted oxycarbonyl groups (e.g. C_{2-8} alkyloxycarbonyl or C_{7-8}-aralkyloxy-carbonyl groups such as methyloxycarbonyl, tert-butyloxycarbonyl, benzyloxycarbonyl, etc.).

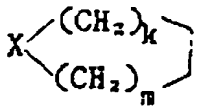
Each of these acyl groups may optionally have 1 to 3, preferably 1 to 2, substituents such as halogen (e.g. fluoro, chloro, bromo, iodo), amino, C_{1-6} alkyl or C_{3-6} cycloalkyl-substituted primary or secondary amino (e.g. methylamino, ethylamino, propylamino, cyclohexylamino, dimethylamino, diethylamino, diisopropylamino, dicyclohexylamino), C_{1-4} alkoxy (e.g. methoxy, ethoxy, propoxy) and so on.

X is preferably R^1-N< and especially R^1 is preferably hydrogen, methyl, ethyl, benzyl, acetyl, benzoyl, methoxycarbonyl or ethoxycarbonyl.

R^2 is preferably a benzyl or α-naphthylmethyl group which is either unsubstituted or substituted by 1 or 2 substituents selected from the group consisting of halogen (e.g. fluoro, chloro), methyl, nitro and/or methoxy and more preferable examples of R^2 include an unsubstituted benzyl.

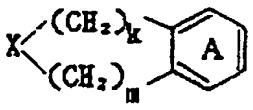
The substituent on ring A is preferably fluoro, chloro, trifluoromethyl, methyl or methoxy, and more preferably fluoro.

The preferred k and m are such that when the sum of k and m is a whole number of 2 to 6; that is when



forms a 5 to 9 membered ring.

The preferred combination of k and m is such that when k is 0, m is 2, 3, 4 or 5; when k is 1, m is 1, 2 or 3; or when k is 2, m is 2. Thus, the preferred nitrogen-containing condensed heterocyclic rings which are represented by

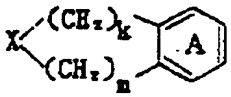


(X=R^1-N<)

are 2,3-dihydro-1H-indole, 1,2,3,4-tetrahydroquinoline, 2,3,4,5-tetrahydro-1H-1-benzazepine, 2,3-dihydro-1H-isoindole, 1,2,3,4-tetrahydroisoquinoline, 2,3,4,5-tetrahydro-1H-2-benzazepine, 2,3,4,5-tetrahydro-1H-3-benzazepine, 1,2,3,4,5,6-hexahydro-1-benzazocine, 1,2,3,4,5,6-hexahydro-2-benzazocine, 1,2,3,4,5,6-hexahydro-

3-benzazocine,2,3,4,5,6,7-hexahydro-1H-1-benzazonine, 2,3,4,5,6,7-hexahydro-1H-2-benzazonine, 2,3,4,5,6,7-hexahydro-1H-3-benzazonine, 2,3,4,5,6,7-hexahydro-1H-4-benzazonine.

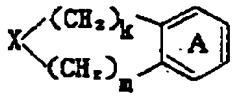
The preferred oxygen-containing condensed heterocyclic rings which are represented by



(X=O)

are 2,3-dihydrobenzofuran, 1,3-dihydroisobenzofuran, 3,4-dihydro-2H-1-benzopyran, 2,3,4,5-tetrahydro-1-benzoxepin, 1,3,4,5-tetrahydro-2-benzoxepin, 1,2,4,5-tetrahydro-3-benzoxepin, 3,4,5,6-tetrahydro-2H-1-benzoxocin, 3,4,5,6-tetrahydro-1H-2-benzoxocin, 1,4,5,6-tetrahydro-2H-3-benzoxocin, 2,3,4,5,6,7-hexahydro-1-benzoxonin, 1,3,4,5,6,7-hexahydro-2-benzoxonin, 1,2,4,5,6,7-hexahydro-4-benzoxonin, 1,2,3,5,6,7-hexahydro-4-benzoxonin.

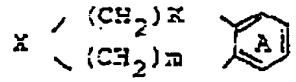
The preferred sulfur-containing condensed heterocyclic rings which are represented by



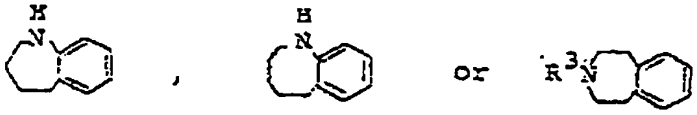
(X=S)

are 2,3-dihydro[b]thiophen, 1,3-dihydrobenzo[c]thiophen, 3,4-dihydro-2H-1-benzothiopyran, 3,4-dihydro-1H-2-benzothiopyran, 2,3,4,5-tetrahydro-1-benzothiepin, 1,3,4,5-tetrahydro-2-benzothiepin, 1,2,4,5-tetrahydro-3-benzothiepin, 3,4,5,6-tetrahydro-2H-1-benzothiocin, 3,4,5,6-tetrahydro-1H-2-benzothiocin, 1,4,5,6-tetrahydro-2H-3-benzothiocin, 2,3,4,5,6,7-hexahydro-1-benzothionin, 1,3,4,5,6,7-hexahydro-2-benzothionin, 1,2,4,5,6,7-hexahydro-3-benzothionin, 1,2,3,5,6,7-hexahydro-4-benzothionin.

The more preferred heterocyclic rings which are represented by



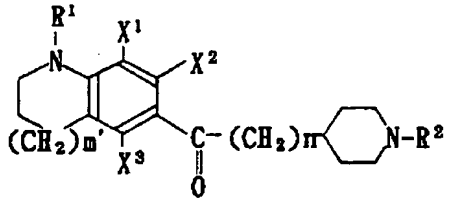
wherein each symbol is as defined above, include



wherein R^3 is a hydrogen atom or a C_{1-3} alkyl group. The C_{1-3} alkyl group of R^3 includes methyl, ethyl, propyl and iso-propyl.

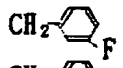
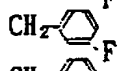
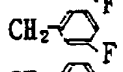
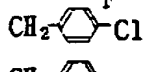
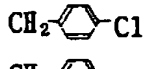
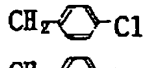
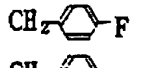
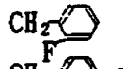
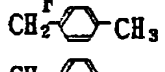
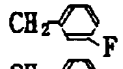
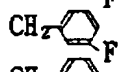
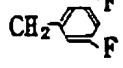
The preferred example of n is 1,2 or 3, and more preferably 2.

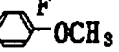
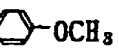
Specifically, the following compounds of formula (I) and their salts thereof are preferred.



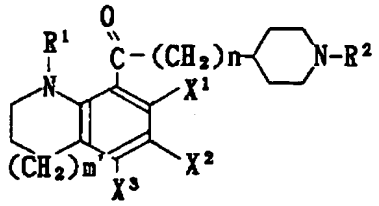
No.	m'	n	X^1	X^2	X^3	R^1	R^2
1	1	2	H	H	H	H	CH_2Ph
2	1	2	H	H	H	CH_3	CH_2Ph
3	1	2	H	H	H	C_2H_5	CH_2Ph
4	1	2	H	H	H	CH_2Ph	CH_2Ph
5	1	2	H	H	H	$COCH_3$	CH_2Ph
6	1	2	H	H	H	COPh	CH_2Ph
7	1	2	CH_3	H	H	CH_3	CH_2Ph
8	1	2	H	F	CH_3	CH_3	CH_2Ph
9	1	2	H	Cl	H	CH_3	CH_2Ph
10	1	2	CH_3	OCH_3	H	CH_3	CH_2Ph
11	1	2	OCH_3	F	H	CH_3	CH_2Ph
12	1	2	F	F	H	CH_3	CH_2Ph
13	1	2	OCH_3	Cl	H	CH_3	CH_2Ph
14	1	2	F	F	OCH_3	CH_3	CH_2Ph
15	1	2	Cl	CH_3	F	CH_3	CH_2Ph
16	1	2	H	H	H	CH_3	CH_2CH_2Ph
17	1	2	H	H	H	CH_3	CH_2-(4-F-Ph)

No.	m'	n	X^1	X^2	X^3	R^1	R^2
18	1	2	H	H	H	CH_2Ph	
19	1	2	H	H	H	H	
20	1	2	H	H	H	H	
21	1	2	H	H	H	CH_3	
22	1	2	H	H	H	CH_3	
23	1	2	H	H	H	CH_3	
24	1	2	CF_3	F	H	H	
25	1	2	Cl	H	H	H	
26	1	2	OCH_3	F	CH_3	CH_3	
27	1	2	H	F	Cl	CH_3	
28	1	2	CH_3	H	H	H	
29	1	2	Cl	H	H	H	
30	1	2	CH_3	H	H	CH_3	
31	1	2	F	H	Cl	CH_3	
32	1	2	OCH_3	Cl	H	CH_3	
33	1	2	OCH_3	H	H	CH_3	
34	1	1	H	H	H	H	CH_2Ph
35	1	1	H	H	H	CH_3	CH_2Ph
36	1	3	H	H	H	H	CH_2Ph
37	1	3	H	H	H	CH_3	CH_2Ph
38	0	2	H	H	H	H	CH_2Ph
39	0	2	H	H	H	CH_3	CH_2Ph
40	0	2	H	H	H	C_2H_5	CH_2Ph

No.	m'	n	X^1	X^2	X^3	R^1	R^2
41	0	2	H	H	H	CH_2Ph	CH_2Ph
42	0	2	H	H	H	$COCH_3$	CH_2Ph
43	0	2	H	H	H	COPh	CH_2Ph
44	0	2	F	H	H	CH_3	CH_2Ph
45	0	2	F	H	CH_3	CH_3	CH_2Ph
46	0	2	CH_3	H	H	CH_3	CH_2Ph
47	0	2	OCH_3	H	H	CH_3	CH_2Ph
48	0	2	Cl	H	H	CH_3	CH_2Ph
49	0	2	OCH_3	Cl	H	CH_3	CH_2Ph
50	0	2	F	H	OCH_3	CH_3	CH_2Ph
51	0	2	Cl	CH_3	F	CH_3	CH_2Ph
52	0	2	H	H	H	H	
53	0	2	H	H	H	CH_3	
54	0	2	H	H	H	CH_2Ph	
55	0	2	H	H	H	H	
56	0	2	H	H	H	CH_3	
57	0	2	H	H	H	CH_2Ph	
58	0	2	H	H	H	H	
59	0	2	H	H	H	H	
60	0	2	H	H	H	CH_3	
61	0	2	F	H	H	H	
62	0	2	Cl	H	H	H	
63	0	2	H	H	CH_3	CH_3	

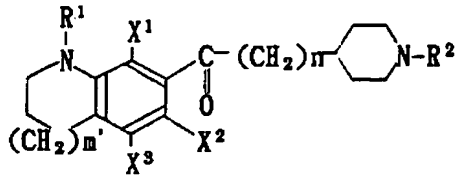
No.	m'	n	X^1	X^2	X^3	R^1	R^2
64	0	2	F	H	Cl	CH_3	
65	0	2	F	H	H	H	
66	0	2	Cl	H	H	H	
67	0	2	H	H	CH_3	CH_3	
68	0	2	F	H	Cl	CH_3	
69	0	2	OCH_3	OCH_3	H	CH_3	
70	2	2	H	H	H	H	CH_2Ph
71	2	2	H	H	H	CH_3	CH_2Ph
72	2	2	H	H	H	C_2H_5	CH_2Ph
73	2	2	F	H	H	H	CH_2Ph
74	2	2	F	H	H	CH_3	CH_2Ph
75	2	2	F	H	H	CH_2Ph	CH_2Ph
76	2	2	F	H	Cl	CH_3	CH_2Ph
77	2	2	F	H	CH_3	CH_3	CH_2Ph
78	2	2	CH_3	H	H	CH_3	CH_2Ph
79	2	2	OCH_3	H	H	CH_3	CH_2Ph
80	2	2	Cl	H	H	CH_3	CH_2Ph
81	2	2	OCH_3	Cl	H	CH_3	CH_2Ph
82	2	2	F	H	OCH_3	CH_3	CH_2Ph
83	2	2	Cl	CH_3	F	CH_3	CH_2Ph
84	2	2	H	H	H	H	
85	2	2	H	H	H	CH_3	
86	2	2	H	H	H	CH_2Ph	

No.	m'	n	X^1	X^2	X^3	R^1	R^2
87	2	2	H	H	H	H	
88	1	2	H	H	H	CH_3	H
89	1	2	H	H	H	H	C_2H_5



No.	m'	n	X^1	X^2	X^3	R^1	R^2
90	1	2	H	H	H	H	CH_2Ph
91	1	2	H	H	H	CH_3	CH_2Ph
92	1	2	H	H	H	C_2H_5	CH_2Ph
93	1	2	H	H	H	CH_2Ph	CH_2Ph
94	1	2	H	H	H	$COCH_3$	CH_2Ph
95	1	2	H	H	H	COPh	CH_2Ph
96	1	2	H	F	H	CH_3	CH_2Ph
97	1	2	H	F	CH_3	CH_3	CH_2Ph
98	1	2	H	OCH_3	OCH_3	CH_3	CH_2Ph
99	1	2	H	F	Cl	CH_3	CH_2-(2-F-Ph)
100	1	2	H	F	H	H	CH_2-(2-F-Ph)
101	1	2	Cl	F	H	H	CH_2-(2-F-Ph)
102	1	2	H	Cl	CH_3	CH_3	CH_2-(2-F-Ph)
103	1	2	H	OCH_3	H	CH_3	CH_2-(2-F-Ph)
104	1	1	H	H	H	H	CH_2Ph
105	1	1	H	H	H	CH_3	CH_2Ph
106	1	3	H	H	H	H	CH_2Ph
107	1	3	H	H	H	CH_3	CH_2Ph

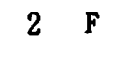
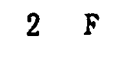
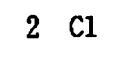
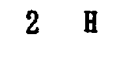
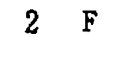
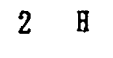
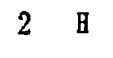
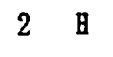
No.	m'	n	X^1	X^2	X^3	R^1	R^2
108	0	2	H	H	H	H	CH_2Ph
109	0	2	H	H	H	CH_3	CH_2Ph
110	0	2	H	H	H	C_2H_5	CH_2Ph
111	0	2	H	H	H	CH_2Ph	CH_2Ph
112	0	2	H	H	H	$COCH_3$	CH_2Ph
113	0	2	H	H	H	COPh	CH_2Ph
114	0	2	H	F	H	CH_3	CH_2Ph
115	0	2	H	F	CH_3	CH_3	CH_2Ph
116	0	2	H	F	H	CH_3	
117	2	2	H	OCH_3	H	CH_3	CH_2Ph
118	2	2	H	CH_3	H	CH_3	CH_2Ph
119	2	2	H	H	H	H	
120	2	2	H	H	H	CH_3	
121	2	2	H	H	H	CH_2Ph	
122	2	2	H	F	H	CH_3	



No.	m'	n	X^1	X^2	X^3	R^1	R^2
123	1	2	H	H	H	H	CH_2Ph
124	1	2	H	H	H	CH_3	CH_2Ph
125	1	2	H	H	H	C_2H_5	CH_2Ph
126	1	2	H	H	H	CH_2Ph	CH_2Ph
127	1	2	H	H	H	$COCH_3$	CH_2Ph
128	1	2	H	H	H	COPh	CH_2Ph
129	1	2	H	H	CH_3	CH_3	CH_2Ph
130	1	2	H	F	CH_3	CH_3	CH_2Ph
131	1	2	F	H	F	CH_3	CH_2Ph
132	1	2	H	OCH_3	OCH_3	CH_3	CH_2Ph
133	1	2	OCH_3	H	H	CH_3	CH_2Ph
134	1	2	H	F	F	CH_3	CH_2Ph
135	1	2	OCH_3	Cl	H	CH_3	CH_2Ph
136	1	2	F	H	OCH_3	CH_3	CH_2Ph
137	1	2	Cl	CH_3	F	CH_3	CH_2Ph
138	1	2	H	H	H	CH_3	CH_2CH_2Ph
139	1	2	H	H	H	CH_3	

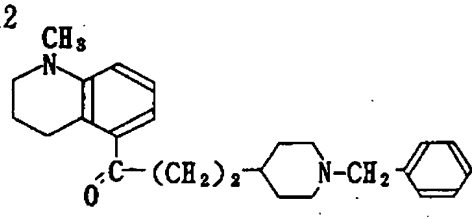
No.	m'	n	X^1	X^2	X^3	R^1	R^2
140	1	2	H	H	H	CH_2Ph	
141	1	2	H	H	H	H	
142	1	2	H	H	H	H	
143	1	2	H	H	H	CH_3	
144	1	2	H	H	H	CH_3	
145	1	2	H	H	H	CH_3	
146	1	2	H	H	CH_3	H	
147	1	2	Cl	H	H	H	
148	1	2	H	H	CH_3	CH_3	
149	1	2	H	F	Cl	CH_3	
150	1	2	F	H	CH_3	H	
151	1	2	Cl	H	F	H	
152	1	2	H	H	CH_3	CH_3	
153	1	2	F	H	Cl	CH_3	
154	1	2	H	H	H	CH_3	H
155	1	2	H	H	H	CH_2Ph	H
156	1	1	H	H	H	H	CH_2Ph
157	1	1	H	H	H	CH_3	CH_2Ph
158	1	3	H	H	H	H	CH_2Ph
159	1	3	H	H	H	CH_3	CH_2Ph
160	0	2	H	H	H	H	CH_2Ph
161	0	2	H	H	H	CH_3	CH_2Ph
162	0	2	H	H	H	C_2H_5	CH_2Ph

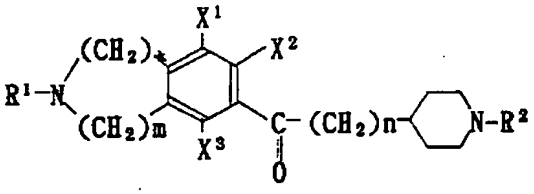
No.	m'	n	X^1	X^2	X^3	R^1	R^2
163	0	2	H	H	H	CH_2Ph	CH_2Ph
164	0	2	H	H	H	$COCH_3$	CH_2Ph
165	0	2	H	H	H	COPh	CH_2Ph
166	0	2	H	F	H	CH_3	CH_2Ph
167	0	2	H	F	CH_3	CH_3	CH_2Ph
168	0	2	CH_3	H	H	CH_3	CH_2Ph
169	0	2	H	OCH_3	H	CH_3	CH_2Ph
170	0	2	H	Cl	H	CH_3	CH_2Ph
171	0	2	OCH_3	Cl	H	CH_3	CH_2Ph
172	0	2	H	F	OCH_3	CH_3	CH_2Ph
173	0	2	Cl	CH_3	F	CH_3	CH_2Ph
174	0	2	H	H	H	H	CH_2-  -F
175	0	2	H	H	H	CH_3	CH_2-  -F
176	0	2	H	H	H	CH_2Ph	CH_2-  -F
177	0	2	H	H	H	H	CH_2-  -Cl
178	0	2	H	H	H	CH_3	CH_2-  -Cl
179	0	2	H	H	H	CH_2Ph	CH_2-  -Cl
180	0	2	H	H	H	H	CH_2-  -F
181	0	2	H	H	H	H	CH_2- 
182	0	2	H	H	H	CH_3	CH_2-  -CH_3
183	0	2	H	F	H	H	CH_2-  -F
184	0	2	H	Cl	H	H	CH_2-  -F
185	0	2	H	F	CH_3	CH_3	CH_2-  -F

No.	m'	n	X^1	X^2	X^3	R^1	R^2
186	0	2	F	F	H	CH_3	
187	0	2	F	H	H	H	
188	0	2	Cl	Cl	H	H	
189	0	2	H	F	CH_3	CH_3	
190	0	2	F	F	H	CH_3	
191	0	2	H	H	H	CH_3	H
192	2	2	H	H	H	H	CH_2Ph
193	2	2	H	H	H	CH_3	CH_2Ph
194	2	2	H	H	H	C_2H_5	CH_2Ph
195	2	2	H	H	F	H	CH_2Ph
196	2	2	H	H	Cl	CH_3	CH_2Ph
197	2	2	F	H	CH_3	CH_2Ph	CH_2Ph
198	2	2	F	H	Cl	CH_3	CH_2Ph
199	2	2	H	H	CH_3	CH_3	CH_2Ph
200	2	2	CH_3	H	H	CH_3	CH_2Ph
201	2	2	OCH_3	H	CH_3	CH_3	CH_2Ph
202	2	2	Cl	H	CH_3	CH_3	CH_2Ph
203	2	2	OCH_3	Cl	CH_3	CH_3	CH_2Ph
204	2	2	F	H	OCH_3	CH_3	CH_2Ph
205	2	2	Cl	CH_3	F	CH_3	CH_2Ph
206	2	2	H	H	H	H	
207	2	2	H	H	H	CH_3	
208	2	2	H	H	H	CH_2Ph	

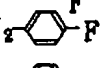
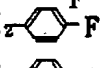
No.	m'	n	X^1	X^2	X^3	R^1	R^2
209	2	2	H	H	CH_3	H	
210	1	2	H	H	H	CH_3	CH_3
211	1	2	H	H	H	C_2H_5	C_2H_5

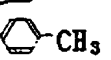
212





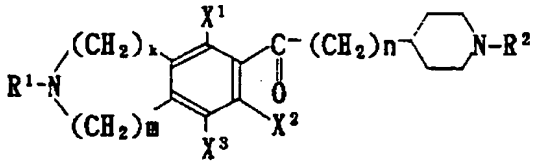
No.	k	m	n	X^1	X^2	X^3	R^1	R^2
213	1	2	2	H	H	H	H	CH_2Ph
214	1	2	2	H	H	H	CH_3	CH_2Ph
215	1	2	2	H	H	H	C_2H_5	CH_2Ph
216	1	2	2	H	H	H	CH_2Ph	CH_2Ph
217	1	2	2	H	H	H	$COCH_3$	CH_2Ph
218	1	2	2	H	H	H	COPh	CH_2Ph
219	1	2	2	H	F	H	CH_3	CH_2Ph
220	1	2	2	H	F	CH_3	CH_3	CH_2Ph
221	1	2	2	CH_3	Cl	H	CH_3	CH_2Ph
222	1	2	2	H	OCH_3	H	CH_3	CH_2Ph
223	1	2	2	OCH_3	F	H	CH_3	CH_2Ph
224	1	2	2	F	F	H	CH_3	CH_2Ph
225	1	2	2	Cl	Cl	H	CH_3	CH_2Ph
226	1	2	2	F	F	OCH_3	CH_3	CH_2Ph
227	1	2	2	Cl	CH_3	F	CH_3	CH_2Ph
228	1	2	2	H	H	H	CH_3	CH_2CH_2Ph
229	1	2	2	H	H	H	CH_3	

No.	k	m	n	X^1	X^2	X^3	R^1	R^2
230	1	2	2	H	H	H	CH_2Ph	
231	1	2	2	H	H	H	H	
232	1	2	2	H	H	H	H	
233	1	2	2	H	H	H	CH_3	
234	1	2	2	H	H	H	CH_3	
235	1	2	2	H	H	H	CH_3	
236	1	2	2	CF_3	F	H	H	
237	1	2	2	Cl	Cl	H	H	
238	1	2	2	H	F	CH_3	CH_3	
239	1	2	2	H	F	Cl	CH_3	
240	1	2	2	CH_3	H	H	H	
241	1	2	2	Cl	Cl	H	H	
242	1	2	2	H	F	CH_3	CH_3	
243	1	2	2	F	OCH_3	Cl	CH_3	
244	1	2	2	H	H	H	CH_2Ph	H
245	1	2	2	H	H	H	CH_3	H
246	1	2	1	H	H	H	H	CH_2Ph
247	1	2	1	H	H	H	CH_3	CH_2Ph
248	1	2	3	H	H	H	H	CH_2Ph
249	1	2	3	H	H	H	CH_3	CH_2Ph
250	1	3	2	H	H	H	H	CH_2Ph
251	1	3	2	H	H	H	CH_3	CH_2Ph
252	1	3	2	H	H	H	C_2H_5	CH_2Ph

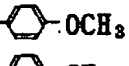
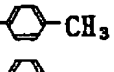
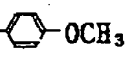
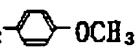
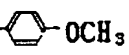
No.	k	m	n	X^1	X^2	X^3	R^1	R^2
253	1	3	2	H	H	H	CH_2Ph	CH_2Ph
254	1	3	2	H	H	H	$COCH_3$	CH_2Ph
255	1	3	2	H	H	H	COPh	CH_2Ph
256	1	3	2	CH_3	H	H	CH_3	CH_2Ph
257	1	3	2	CH_3	H	CH_3	CH_3	CH_2Ph
258	1	3	2	F	F	H	CH_3	CH_2Ph
259	1	3	2	OCH_3	H	H	CH_3	CH_2Ph
260	1	3	2	Cl	H	H	CH_3	CH_2Ph
261	1	3	2	OCH_3	Cl	H	CH_3	CH_2Ph
262	1	3	2	F	H	OCH_3	CH_3	CH_2Ph
263	1	3	2	Cl	CH_3	F	CH_3	CH_2Ph
264	1	3	2	H	H	H	H	
265	1	3	2	H	H	H	CH_3	
266	1	3	2	H	H	H	CH_2Ph	
267	1	3	2	H	H	H	H	
268	1	3	2	H	H	H	CH_3	
269	1	3	2	H	H	H	CH_2Ph	
270	1	3	2	H	H	H	H	
271	1	3	2	H	H	H	H	
272	1	3	2	H	H	H	CH_3	
273	1	3	2	F	H	H	H	
274	1	3	2	Cl	H	H	H	
275	1	3	2	CH_3	H	OH	CH_3	

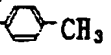
No.	k	m	n	X^1	X^2	X^3	R^1	R^2
276	1	3	2	F	H	Cl	CH_3	
277	1	3	2	F	H	H	H	
278	1	3	2	Cl	H	H	H	
279	1	3	2	CH_3	H	H	CH_3	
280	1	3	2	F	H	Cl	CH_3	
281	1	3	2	CH_3	OCH_3	H	CH_3	H
282	1	1	2	H	H	H	H	CH_2Ph
283	1	1	2	H	H	H	CH_3	CH_2Ph
284	1	1	2	H	H	H	C_2H_5	CH_2Ph
285	2	2	2	H	H	H	H	CH_2Ph
286	2	2	2	H	H	H	CH_3	CH_2Ph
287	2	2	2	H	H	H	CH_2Ph	CH_2Ph
288	2	2	2	F	H	Cl	CH_3	CH_2Ph
289	2	2	2	F	H	CH_3	CH_3	CH_2Ph
290	2	2	2	CH_3	H	H	CH_3	CH_2Ph
291	2	2	2	OCH_3	H	H	CH_3	CH_2Ph
292	2	2	2	Cl	H	H	CH_3	CH_2Ph
293	2	2	2	OCH_3	Cl	H	CH_3	CH_2Ph
294	2	2	2	F	H	OCH_3	CH_3	CH_2Ph
295	2	2	2	Cl	CH_3	F	CH_3	CH_2Ph
296	2	2	2	H	H	H	H	
297	2	2	2	H	H	H	CH_3	
298	2	2	2	H	H	H	CH_2Ph	

No.	k	m	n	X^1	X^2	X^3	R^1	R^2
299	2	2	2	H	H	H	H	H
300	1	2	2	H	H	H	CH_3	H
301	1	2	2	H	H	H	H	C_2H_5



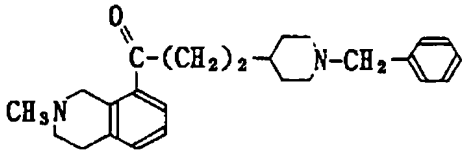
No.	k	m	n	X^1	X^2	X^3	R^1	R^2
302	1	2	2	H	H	H	H	CH_2Ph
303	1	2	2	H	H	H	CH_3	CH_2Ph
304	1	2	2	H	H	H	C_2H_5	CH_2Ph
305	1	2	2	H	H	H	CH_2Ph	CH_2Ph
306	1	2	2	H	H	H	$COCH_3$	CH_2Ph
307	1	2	2	H	H	H	COPh	CH_2Ph
308	1	2	2	H	H	CH_3	CH_3	CH_2Ph
309	1	2	2	F	H	CH_3	CH_3	CH_2Ph
310	1	2	2	H	H	F	CH_3	CH_2Ph
311	1	2	2	H	OCH_3	OCH_3	CH_3	CH_2Ph
312	1	2	2	OCH_3	H	CH_3	CH_3	CH_2Ph
313	1	2	2	H	H	Cl	CH_3	CH_2Ph
314	1	2	2	H	Cl	CH_3	CH_3	CH_2Ph
315	1	2	2	H	F	OCH_3	CH_3	CH_2Ph
316	1	2	2	Cl	CH_3	F	CH_3	CH_2Ph
317	1	2	2	H	H	H	CH_3	CH_2CH_2Ph
318	1	2	2	H	H	H	CH_3	

No.	l	m	n	X^1	X^2	X^3	R^1	R^2
319	1	2	2	H	H	H	CH_2Ph	
320	1	2	2	H	H	H	H	
321	1	2	2	H	H	H	H	
322	1	2	2	H	H	H	CH_3	
323	1	2	2	H	H	H	CH_3	
324	1	2	2	H	H	H	CH_3	
325	1	2	2	H	H	CF_3	H	
326	1	2	2	H	H	Cl	H	
327	1	2	2	H	H	CH_3	CH_3	
328	1	2	2	H	F	Cl	CH_3	
329	1	2	2	F	H	CH_3	H	
330	1	2	2	Cl	H	CH_3	H	
331	1	2	2	H	H	CH_3	CH_3	
332	1	2	2	H	F	Cl	CH_3	
333	1	2	2	H	Cl	CH_3	CH_3	
334	1	2	2	NO_2	OCH_3	OCH_3	CH_3	
335	1	2	1	H	H	H	H	CH_2Ph
336	1	2	1	H	H	H	CH_3	CH_2Ph
337	1	2	3	H	H	H	H	CH_2Ph
338	1	3	3	H	H	H	CH_3	CH_2Ph
339	1	3	2	H	H	H	H	CH_2Ph
340	1	3	2	H	H	H	CH_3	CH_2Ph
341	1	3	2	H	H	H	C_2H_5	CH_2Ph

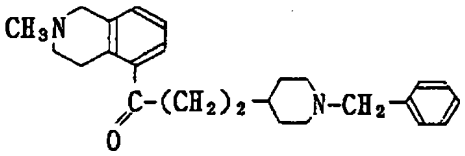
No.	l	m	n	X^1	X^2	X^3	R^1	R^2
342	1	3	2	H	H	H	CH_2Ph	CH_2Ph
343	1	3	2	H	H	H	$COCH_3$	CH_2Ph
344	1	3	2	H	H	H	COPh	CH_2Ph
345	1	3	2	H	H	CH_3	CH_3	CH_2Ph
346	1	3	2	H	F	CH_3	CH_3	CH_2Ph
347	1	3	2	F	H	CH_3	CH_3	CH_2Ph
348	1	3	2	H	H	OCH_3	CH_3	CH_2Ph
349	1	3	2	H	H	Cl	CH_3	CH_2Ph
350	1	3	2	H	Cl	F	CH_3	CH_2Ph
351	1	3	2	H	CH_3	OCH_3	CH_3	CH_2Ph
352	1	3	2	Cl	CH_3	F	CH_3	CH_2Ph
353	1	3	2	H	H	H	H	
354	1	3	2	H	H	H	CH_3	
355	1	3	2	H	H	H	CH_2Ph	
356	1	3	2	H	H	H	H	
357	1	3	2	H	H	H	CH_3	
358	1	3	2	H	H	H	CH_2Ph	
359	1	3	2	H	H	H	H	
360	1	3	2	H	H	H	H	
361	1	3	2	H	H	H	CH_3	
362	1	3	2	H	H	F	H	
363	1	3	2	H	H	Cl	H	
364	1	3	2	H	H	CH_3	CH_3	

No.	l	m	n	X^1	X^2	X^3	R^1	R^2
365	1	3	2	H	H	Cl	CH_3	
366	1	3	2	H	H	OCH_3	H	
367	1	3	2	SCH_3	H	CH_3	H	
368	1	3	2	H	CH_3	CH_3	CH_3	
369	1	3	2	H	H	Cl	CH_3	
370	1	3	2	H	OCH_3	OCH_3	CH_3	
371	1	2	2	H	H	H	H	H
372	1	2	2	H	H	H	CH_3	H
373	1	2	2	H	H	H	C_2H_5	H
374	1	2	2	H	H	H	H	CH_3
375	1	2	2	H	H	H	CH_3	CH_3
376	1	2	2	H	H	H	CH_2Ph	CH_3
377	1	3	2	H	H	H	CH_3	H
378	1	3	2	H	H	CH_3	CH_3	H
379	1	3	2	H	H	F	CH_3	H
380	1	3	2	OCH_3	H	CH_3	CH_3	CH_3
381	1	3	2	H	H	OCH_3	CH_3	CH_3

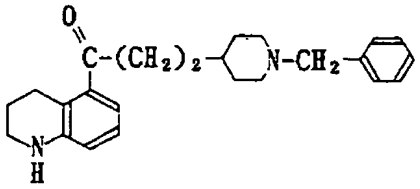
382



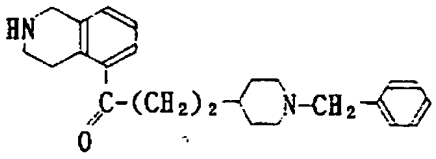
383



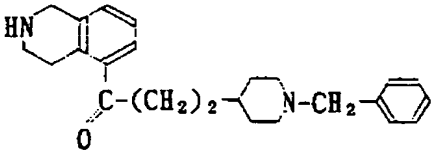
384

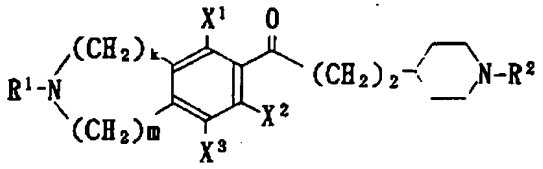


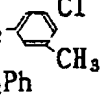
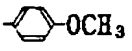
385

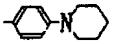


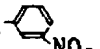
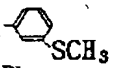
386

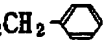


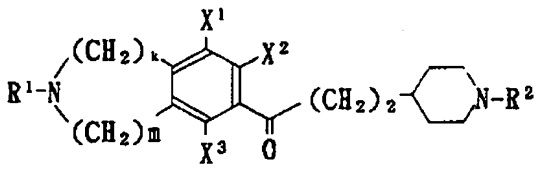


No.	k	m	X^1	X^2	X^3	R^1	R^2
387	0	5	H	H	H	H	CH_2Ph
388	0	5	H	H	H	CH_3	CH_2Ph
389	0	5	H	H	H	C_2H_5	CH_2Ph
390	0	5	H	H	H	CH_2Ph	CH_2Ph
391	0	5	H	H	H	$COCH_3$	CH_2Ph
392	0	5	H	H	H	COPh	CH_2Ph
393	0	5	H	H	H	H	H
394	0	5	H	H	H	H	
395	0	5	CH_3	H	Cl	CH_3	
396	0	5	F	H	OCH_3	CH_3	CH_2Ph
397	1	4	H	H	H	H	CH_2Ph
398	1	4	H	H	H	CH_3	CH_2Ph
399	1	4	H	H	H	C_2H_5	CH_2Ph
400	1	4	H	H	H	CH_2Ph	CH_2Ph
401	1	4	H	H	H	$COCH_3$	CH_2Ph
402	1	4	H	H	H	COPh	CH_2Ph
403	1	4	CH_3	H	CH_3	H	
404	1	4	Cl	H	H	H	CH_2Ph
405	1	4	CH_3	H	F	CH_3	
406	1	4	F	H	OCH_3	CH_3	CH_2Ph
407	2	3	H	H	H	H	CH_2Ph

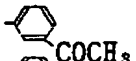
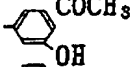
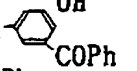
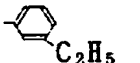
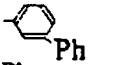
No.	k	m	X^1	X^2	X^3	R^1	R^2
408	2	3	H	H	H	CH_3	CH_2Ph
409	2	3	H	H	H	C_2H_5	CH_2Ph
410	2	3	H	H	H	CH_2Ph	CH_2Ph
411	2	3	H	H	H	$COCH_3$	CH_2Ph
412	2	3	H	H	H	COPh	CH_2Ph
413	2	3	CH_3	H	CH_3	H	
414	2	3	Cl	H	H	H	CH_2Ph
415	2	3	CH_3	H	F	CH_3	
416	2	3	F	H	OCH_3	CH_3	CH_2Ph
417	3	2	H	H	H	H	CH_2Ph
418	3	2	H	H	H	CH_3	CH_2Ph
419	3	2	H	H	H	C_2H_5	CH_2Ph
420	3	2	H	H	H	CH_2Ph	CH_2Ph
421	3	2	H	H	H	$COCH_3$	CH_2Ph
422	3	2	H	H	H	COPh	CH_2Ph
423	3	2	CH_3	H	CH_3	H	
424	3	2	Cl	H	H	H	CH_2Ph
425	3	2	CH_3	H	F	CH_3	
426	3	2	F	H	OCH_3	CH_3	CH_2Ph
427	0	6	H	H	H	H	CH_2Ph
428	0	6	H	H	H	CH_3	CH_2Ph
429	0	6	H	H	H	C_2H_5	CH_2Ph
430	0	6	H	H	H	CH_2Ph	CH_2Ph
431	0	6	H	H	H	$COCH_3$	CH_2Ph
432	0	6	H	H	H	COPh	CH_2Ph
433	0	6	H	H	Cl	H	

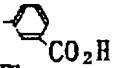
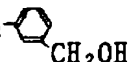
No.	k	m	X^1	X^2	X^3	R^1	R^2
434	0	6	H	H	H	H	
435	0	6	CH_3	H	F	CH_3	
436	0	6	F	H	OCH_3	CH_3	CH_2Ph
437	1	5	H	H	H	H	CH_2Ph
438	1	5	H	H	H	CH_3	CH_2Ph
439	1	5	H	H	H	C_2H_5	CH_2Ph
440	1	5	H	H	H	CH_2Ph	CH_2Ph
441	1	5	H	H	H	$COCH_3$	CH_2Ph
442	1	5	H	H	H	COPh	CH_2Ph
443	1	5	H	H	Cl	H	
444	1	5	H	H	CH_3	H	CH_2Ph
445	1	5	CH_3	H	F	CH_3	
446	1	5	F	H	OCH_3	CH_3	CH_2Ph
457	2	4	H	H	H	H	CH_2Ph
458	2	4	H	H	H	CH_3	CH_2Ph
459	2	4	H	H	H	C_2H_5	CH_2Ph
460	2	4	H	H	H	CH_2Ph	CH_2Ph
461	2	4	H	H	H	$COCH_3$	CH_2Ph
462	2	4	H	H	H	COPh	CH_2Ph
463	2	4	CH_3	H	CH_3	H	
464	2	4	Cl	H	H	H	CH_2Ph
465	2	4	CH_3	H	F	CH_3	
466	2	4	F	H	OCH_3	CH_3	CH_2Ph
467	3	3	H	H	H	H	CH_2Ph
468	3	3	H	H	H	CH_3	CH_2Ph
469	3	3	H	H	H	C_2H_5	CH_2Ph

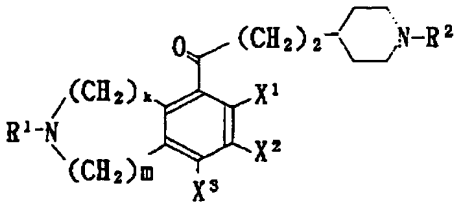
No.	k	m	X^1	X^2	X^3	R^1	R^2
470	3	3	H	H	H	CH_2Ph	CH_2Ph
471	3	3	H	H	H	$COCH_3$	CH_2Ph
472	3	3	H	H	H	COPh	CH_2Ph
473	3	3	H	H	H	H	
474	3	3	H	H	H	H	
475	3	3	CH_3	H	F	CH_3	
476	3	3	F	H	OCH_3	CH_3	CH_2Ph



No.	k	m	X^1	X^2	X^3	R^1	R^2
477	0	5	H	H	H	H	CH_2Ph
478	0	5	H	H	H	CH_3	CH_2Ph
479	0	5	H	H	H	C_2H_5	CH_2Ph
480	0	5	H	H	H	CH_2Ph	CH_2Ph
481	0	5	H	H	H	$COCH_3$	CH_2Ph
482	0	5	H	H	H	COPh	CH_2Ph
483	0	5	H	H	H	H	CH_2-(4-Cl)
484	0	5	H	H	H	H	CH_2-(2-NH_2)
485	0	5	CH_3	H	Cl	CH_3	CH_2-(2-NHAc)
486	0	5	F	H	OCH_3	CH_3	CH_2Ph
487	1	4	H	H	H	H	CH_2Ph
488	1	4	H	H	H	CH_3	CH_2Ph
489	1	4	H	H	H	C_2H_5	CH_2Ph
490	1	4	H	H	H	CH_2Ph	CH_2Ph
501	1	4	H	H	H	$COCH_3$	CH_2Ph
502	1	4	H	H	H	COPh	CH_2Ph
503	1	4	CH_3	H	CH_3	H	CH_2-(2-SO_2CH_3)
504	1	4	Cl	H	H	H	CH_2Ph
505	1	4	CH_3	H	F	CH_3	CH_2-(2-$NHCOCF_3$)
506	1	4	F	H	OCH_3	CH_3	CH_2Ph
507	0	6	H	H	H	H	CH_2Ph

No.	k	m	X^1	X^2	X^3	R^1	R^2
508	0	6	H	H	H	CH_3	CH_2Ph
509	0	6	H	H	H	C_2H_5	CH_2Ph
510	0	6	H	H	H	CH_2Ph	CH_2Ph
511	0	6	H	H	H	$COCH_3$	CH_2Ph
512	0	6	H	H	H	COPh	CH_2Ph
513	0	6	H	H	Cl	H	
514	0	6	H	H	H	H	
515	0	6	CH_3	H	F	CH_3	
516	0	6	F	H	OCH_3	CH_3	CH_2Ph
517	1	5	H	H	H	H	CH_2Ph
518	1	5	H	H	H	CH_3	CH_2Ph
519	1	5	H	H	H	C_2H_5	CH_2Ph
520	1	5	H	H	H	CH_2Ph	CH_2Ph
521	1	5	H	H	H	$COCH_3$	CH_2Ph
522	1	5	H	H	H	COPh	CH_2Ph
523	1	5	H	H	Cl	H	
524	1	5	H	H	CH_3	H	CH_2Ph
525	1	5	CH_3	H	F	CH_3	
526	1	5	F	H	OCH_3	CH_3	CH_2Ph
527	2	4	H	H	H	H	CH_2Ph
528	2	4	H	H	H	CH_3	CH_2Ph
529	2	4	H	H	H	C_2H_5	CH_2Ph
530	2	4	H	H	H	CH_2Ph	CH_2Ph
531	2	4	H	H	H	$COCH_3$	CH_2Ph
532	2	4	H	H	H	COPh	CH_2Ph

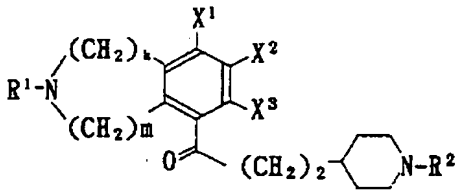
No.	k	m	X^1	X^2	X^3	R^1	R^2
533	2	4	CH_3	H	CH_3	H	
534	2	4	Cl	H	H	H	CH_2Ph
535	2	4	CH_3	H	F	CH_3	
536	2	4	F	H	OCH_3	CH_3	CH_2Ph



No.	k	m	X^1	X^2	X^3	R^1	R^2
537	1	1	H	H	H	H	CH_2Ph
538	1	1	H	H	H	CH_3	CH_2Ph
539	1	1	H	H	CH_3	H	CH_2Ph
540	1	1	H	H	Cl	H	CH_2Ph
541	1	1	H	H	H	$COCH_3$	CH_2Ph
542	1	1	H	H	OCH_3	CH_3	CH_2Ph
543	1	1	H	H	Cl	H	H
544	1	2	H	H	Cl	H	CH_2Ph
545	1	2	H	H	CH_3	H	CH_2Ph
546	1	2	CH_3	H	F	CH_3	CH_2Ph
547	1	2	F	H	OCH_3	C_2H_5	CH_2Ph
548	1	2	H	H	CH_3	H	H
549	2	1	H	H	Cl	H	CH_2Ph
550	2	1	H	H	CH_3	H	CH_2Ph
551	2	1	CH_3	H	F	CH_3	CH_2Ph
552	2	1	F	H	$COCH_3$	C_2H_5	CH_2Ph
553	2	1	H	H	Cl	H	H
554	1	3	H	H	H	H	CH_2Ph
555	1	3	H	H	CH_3	H	CH_2Ph
556	1	3	H	H	Cl	H	CH_2Ph
557	1	3	H	H	H	CH_3	CH_2Ph
558	2	2	H	H	H	H	CH_2Ph

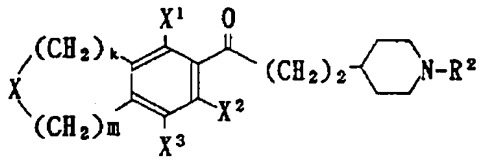
No.	k	m	X^1	X^2	X^3	R^1	R^2
559	2	2	H	H	CH_3	H	CH_2Ph
560	2	2	H	H	Cl	H	CH_2Ph
561	2	2	H	H	H	CH_3	CH_2Ph
562	3	1	H	H	H	H	CH_2Ph
563	3	1	H	H	CH_3	H	CH_2Ph
564	3	1	H	H	Cl	H	CH_2Ph
565	3	1	H	H	H	CH_3	CH_2Ph
566	0	5	H	H	H	H	CH_2Ph
567	0	5	H	H	CH_3	H	CH_2Ph
568	0	5	H	H	Cl	H	CH_2Ph
569	0	5	H	H	H	CH_3	CH_2Ph
570	1	4	H	H	H	H	CH_2Ph
571	1	4	H	H	CH_3	H	CH_2Ph
572	1	4	H	H	Cl	H	CH_2Ph
573	1	4	H	H	H	CH_3	CH_2Ph
574	2	3	H	H	H	H	CH_2Ph
575	2	3	H	H	CH_3	H	CH_2Ph
576	2	3	H	H	Cl	H	CH_2Ph
577	2	3	H	H	H	CH_3	CH_2Ph
578	3	2	H	H	H	H	CH_2Ph
579	3	2	H	H	CH_3	H	CH_2Ph
580	3	2	H	H	Cl	H	CH_2Ph
581	3	2	H	H	H	CH_3	CH_2Ph
582	0	6	H	H	H	H	CH_2Ph
583	0	6	H	H	CH_3	H	CH_2Ph
584	0	6	H	H	Cl	H	CH_2Ph
585	0	6	H	H	H	CH_3	CH_2Ph

No.	k	m	X^1	X^2	X^3	R^1	R^2
586	1	5	H	H	H	H	CH_2Ph
587	1	5	H	H	CH_3	H	CH_2Ph
588	1	5	H	H	Cl	H	CH_2Ph
589	1	5	H	H	H	CH_3	CH_2Ph
590	2	4	H	H	H	H	CH_2Ph
591	2	4	H	H	CH_3	H	CH_2Ph
592	2	4	H	H	Cl	H	CH_2Ph
593	2	4	H	H	H	CH_3	CH_2Ph
594	3	3	H	H	H	H	CH_2Ph
595	3	3	H	H	CH_3	H	CH_2Ph
596	3	3	H	H	Cl	H	CH_2Ph
597	3	3	H	H	H	CH_3	CH_2Ph



No.	k	m	X^1	X^2	X^3	R^1	R^2
598	0	2	CH_3	H	H	H	CH_2Ph
599	0	2	Cl	H	H	H	CH_2Ph
600	0	2	H	H	H	$COCH_3$	CH_2Ph
601	0	2	OCH_3	H	H	CH_3	CH_2Ph
602	0	2	CH_3	H	H	H	H
603	0	3	H	H	H	H	CH_2Ph
604	0	3	H	H	H	CH_3	CH_2Ph
605	0	3	CH_3	H	H	CH_3	CH_2Ph
606	0	3	OCH_3	H	H	H	CH_2Ph
607	0	3	H	H	H	H	H
608	0	5	Cl	H	H	H	CH_2Ph
609	0	5	H	H	H	H	CH_2Ph
610	0	5	CH_3	H	H	CH_3	CH_2Ph
611	0	5	OCH_3	H	H	H	CH_2Ph
612	0	5	H	H	H	H	H
613	1	4	H	H	H	H	CH_2Ph
614	1	4	CH_3	H	H	H	CH_2Ph
615	1	4	OCH_3	H	H	H	CH_2Ph
616	1	4	H	H	H	CH_3	CH_2Ph
617	0	6	H	H	H	H	CH_2Ph
618	0	6	CH_3	H	H	H	CH_2Ph
619	0	6	Cl	H	H	H	CH_2Ph

No.	k	m	X^1	X^2	X^3	R^1	R^2
620	0	6	H	H	H	CH_3	CH_2Ph
621	0	6	H	H	H	H	CH_2Ph
622	0	6	H	H	H	CH_2Ph	CH_2Ph
623	0	6	H	H	H	C_2H_5	CH_2Ph
624	0	6	H	H	H	COPh	CH_2Ph
625	0	6	H	H	H	$COCH_3$	CH_2Ph
626	0	6	H	H	H	COPh	CH_2Ph
627	0	6	F	H	H	CH_3	CH_2Ph
628	0	6	F	H	CH_3	H	CH_2Ph
629	0	6	CH_3	H	H	H	H
630	1	5	H	H	H	H	CH_2Ph
631	1	5	CH_3	H	H	H	CH_2Ph
632	1	5	Cl	H	H	H	CH_2Ph
633	1	5	H	H	H	CH_3	CH_2Ph
634	2	4	H	H	H	H	CH_2Ph
635	2	4	CH_3	H	H	H	CH_2Ph
636	2	4	OCH_3	H	H	H	CH_2Ph
637	2	4	H	H	H	CH_3	CH_2Ph

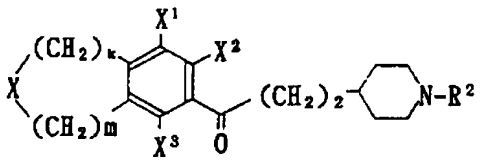


No.	X	k	m	X^1	X^2	X^3	R^2
638	O	0	2	H	H	H	CH_2Ph
639	O	0	2	H	H	CH_3	CH_2Ph
640	O	0	2	H	H	H	H
641	O	1	1	H	H	H	CH_2Ph
642	O	1	1	H	H	CH_3	CH_2Ph
643	O	1	1	H	H	OCH_3	CH_2Ph
644	O	0	3	H	H	H	CH_2Ph
645	O	0	3	H	H	Cl	CH_2Ph
646	O	0	3	H	H	OCH_3	CH_2Ph
647	O	1	2	H	H	C_2H_5	CH_2Ph
648	O	1	2	H	H	H	H
649	O	1	2	H	CH_3	H	CH_2
650	O	2	1	H	H	H	CH_2Ph
651	O	2	1	H	H	CH_3	CH_2Ph
652	O	2	1	H	H	C_2H_5	CH_2Ph
653	O	0	4	H	H	H	H
654	O	0	4	H	H	H	CH_2Ph
655	O	0	4	H	H	CH_3	CH_2Ph
656	O	1	3	H	H	H	CH_2Ph
657	O	1	3	H	H	CH_3	CH_2Ph
658	O	1	3	H	H	H	CH_3
659	O	2	2	H	CH_3	H	CH_2Ph

No.	X	k	m	X^1	X^2	X^3	R^2
660	O	2	2	H	H	H	CH_2Ph
661	O	2	2	H	H	OH	CH_2Ph
662	O	3	1	H	H	H	CH_2Ph
663	O	3	1	H	H	F	CH_2Ph
664	O	3	1	H	OH	Cl	CH_2Ph
665	O	0	5	H	H	CH_3	CH_2Ph
666	O	0	5	H	H	H	CH_2Ph
667	O	1	4	H	OCH_3	H	CH_2Ph
668	O	1	4	H	H	H	CH_2Ph
669	O	2	3	H	H	H	CH_2Ph
670	O	2	3	H	H	OH	CH_2Ph
671	O	3	2	H	CH_3	H	CH_2Ph
672	O	3	2	H	Cl	CH_3	CH_2Ph
673	O	0	6	H	H	H	CH_2Ph
674	O	0	6	H	H	H	H
675	O	1	5	OH	H	H	CH_2Ph
676	O	1	5	H	H	H	CH_2Ph
677	O	2	4	H	H	CH_3	CH_2Ph
678	O	2	4	H	H	H	CH_2Ph
679	O	3	3	H	CH_3	H	CH_2Ph
680	O	3	3	H	H	H	CH_2Ph
681	S	0	2	H	H	H	CH_2Ph
682	S	0	2	H	H	CH_3	CH_2Ph
683	S	0	2	H	H	H	H
684	S	1	1	H	H	H	CH_2Ph
685	S	1	1	H	H	CH_3	CH_2Ph
686	S	1	1	H	H	OCH_3	CH_2Ph

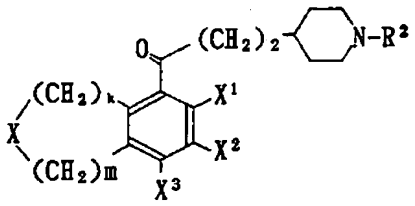
No.	X	k	m	X^1	X^2	X^3	R^2
687	S	0	3	H	H	H	CH_2Ph
688	S	0	3	H	H	Cl	CH_2Ph
689	S	0	3	H	H	OCH_3	CH_2Ph
690	S	1	2	H	H	C_2H_5	CH_2Ph
691	S	1	2	H	H	H	H
692	S	1	2	H	CH_3	H	CH=CH- 
693	S	2	1	H	H	H	CH_2Ph
694	S	2	1	H	H	CH_3	CH_2Ph
695	S	2	1	H	H	C_2H_5	CH_2Ph
696	S	0	4	H	H	H	H
697	S	0	4	H	H	H	CH_2Ph
698	S	0	4	H	H	CH_3	CH_2Ph
699	S	1	3	H	H	H	CH_2Ph
700	S	1	3	H	H	CH_3	CH_2Ph
701	S	1	3	H	H	H	CH_3
702	S	2	2	H	CH_3	H	CH_2Ph
703	S	2	2	H	H	H	CH_2Ph
704	S	2	2	H	H	OH	CH_2Ph
705	S	3	1	H	H	H	CH_2Ph
706	S	3	1	H	H	F	CH_2Ph
707	S	3	1	H	OH	Cl	CH_2Ph
708	S	0	5	H	H	CH_3	CH_2Ph
709	S	0	5	H	H	H	CH_2Ph
710	S	1	4	H	OCH_3	H	CH_2Ph
711	S	1	4	H		H	CH_2Ph
712	S	2	3	H	H	H	CH_2Ph
713	S	2	3	H	H	OH	CH_2Ph

No.	X	k	m	X^1	X^2	X^3	R^2
714	S	3	2	H	CH_3	H	CH_2Ph
715	S	3	2	H	Cl	CH_3	CH_2Ph
716	S	0	6	H	H	H	CH_2Ph
717	S	0	6	H	H	H	H
718	S	1	5	OH	H	H	CH_2Ph
719	S	1	5	H	H	H	CH_2Ph
720	S	2	4	H	H	CH_3	CH_2Ph
721	S	2	4	H	H	H	CH_2Ph
722	S	3	3	H	CH_3	H	CH_2Ph
723	S	3	3	H	H	H	CH_2Ph



No.	X	k	m	X^1	X^2	X^3	R^2
724	O	0	2	H	H	H	CH_2Ph
725	O	0	2	CH_3	H	H	CH_2Ph
726	O	0	2	H	H	H	H
727	O	0	3	H	H	H	CH_2Ph
728	O	0	3	OCH_3	H	CH_3	CH_2Ph
729	O	0	3	OH	H	OCH_3	CH_2Ph
730	O	0	4	H	H	H	CH_2Ph
731	O	0	4	Cl	H	H	CH_2Ph
732	O	0	4	F	H	H	CH_2Ph
733	O	1	4	H	H	H	CH_2Ph
734	O	1	4	CH_3	Cl	H	CH_2Ph
735	O	0	5	H	H	H	CH_2Ph
736	O	0	5	H	CH_3	H	CH_2Ph
737	O	2	4	OH	H	H	CH_2Ph
738	O	2	4	H	H	H	CH_2Ph
739	O	1	5	H	H	H	CH_2Ph
740	O	0	6	H	H	H	CH_2Ph
741	S	0	2	H	H	H	CH_2Ph
742	S	0	2	CH_3	H	H	CH_2Ph
743	S	0	2	H	H	H	H
744	S	0	3	H	H	H	CH_2Ph
745	S	0	3	OCH_3	H	CH_3	CH_2Ph

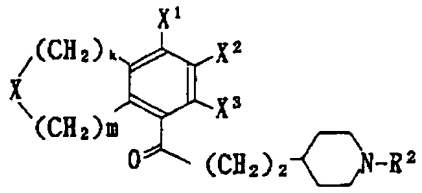
No.	X	k	m	X^1	X^2	X^3	R^2
746	S	0	3	OH	H	OCH_3	CH_2Ph
747	S	0	4	H	H	H	CH_2Ph
748	S	0	4	Cl	H	H	CH_2Ph
749	S	0	4	F	H	H	CH_2Ph
750	S	1	4	H	H	H	CH_2Ph
751	S	1	4	CH_3	Cl	H	CH_2Ph
752	S	0	5	H	H	H	CH_2Ph
753	S	0	5	H	CH_3	H	CH_2Ph
754	S	2	4	OH	H	H	CH_2Ph
755	S	2	4	H	H	H	CH_2Ph
756	S	1	5	H	H	H	CH_2Ph
757	S	0	6	H	H	H	CH_2Ph



No.	X	k	m	X^1	X^2	X^3	R^2
758	O	0	2	H	H	H	CH_2Ph
759	O	0	2	H	H	H	CH_2Ph
760	O	1	1	H	H	H	CH_2Ph
761	O	1	1	OCH_3	H	CH_3	CH_2Ph
762	O	0	3	H	H	H	CH_2Ph
763	O	0	3	H	H	Cl	CH_2Ph
764	O	1	2	H	H	H	CH_2Ph
765	O	1	2	H	Cl	CH_3	CH_2Ph
766	O	2	1	H	H	H	CH_2Ph
767	O	2	1	H	CH_3	H	CH_2Ph
768	O	0	4	H	H	OH	CH_2Ph
769	O	0	4	H	H	H	CH_2Ph
770	O	1	3	H	H	H	CH_2Ph
771	O	1	3	H	H	Cl	CH_2Ph
772	O	2	2	H	H	H	CH_2Ph
773	O	2	2	OCH_3	H	CH_3	CH_2Ph
774	O	3	1	H	H	H	CH_2Ph
775	O	3	1	H	H	Cl	CH_2Ph
776	O	0	5	H	H	H	CH_2Ph
777	O	0	5	H	Cl	CH_3	CH_2Ph
778	O	1	4	H	H	H	CH_2Ph
779	O	1	4	H	CH_3	H	CH_2Ph

No.	X	k	m	X^1	X^2	X^3	R^2
780	O	2	3	H	H	OH	CH_2Ph
781	O	2	3	H	H	H	CH_2Ph
782	O	3	2	H	H	H	CH_2Ph
783	O	3	2	H	H	F	CH_2Ph
784	O	0	6	H	H	H	CH_2Ph
785	O	0	6	H	Cl	CH_3	CH_2Ph
786	O	1	5	H	H	H	CH_2Ph
787	O	1	5	H	CH_3	H	CH_2Ph
788	O	2	4	H	H	OH	CH_2Ph
789	O	2	4	H	H	H	CH_2Ph
790	O	3	3	H	H	H	CH_2Ph
791	O	3	3	H	H	F	CH_2Ph
792	S	0	3	H	H	H	CH_2Ph
793	S	0	2	H	H	H	CH_2Ph
794	S	1	1	H	H	H	CH_2Ph
795	S	1	1	OCH_3	H	CH_3	CH_2Ph
796	S	0	3	H	H	H	CH_2Ph
797	S	0	3	H	H	Cl	CH_2Ph
798	S	1	2	H	H	H	CH_2Ph
799	S	1	2	H	Cl	CH_3	CH_2Ph
800	S	2	1	H	H	H	CH_2Ph
801	S	2	1	H	CH_3	H	CH_2Ph
802	S	0	4	H	H	OH	CH_2Ph
803	S	0	4	H	H	H	CH_2Ph
804	S	1	3	H	H	H	CH_2Ph
805	S	1	3	H	H	Cl	CH_2Ph
806	S	2	2	H	H	H	CH_2Ph

No.	X	k	m	X^1	X^2	X^3	R^2
807	S	2	2	OCH_3	H	CH_3	CH_2Ph
808	S	3	1	H	H	H	CH_2Ph
809	S	3	1	H	H	Cl	CH_2Ph
810	S	0	5	H	H	H	CH_2Ph
811	S	0	5	H	Cl	CH_3	CH_2Ph
812	S	1	4	H	H	H	CH_2Ph
813	S	1	4	H	CH_3	H	CH_2Ph
814	S	2	3	H	H	OH	CH_2Ph
815	S	2	3	H	H	H	CH_2Ph
816	S	3	2	H	H	H	CH_2Ph
817	S	3	2	H	H	F	CH_2Ph
818	S	0	6	H	H	H	CH_2Ph
819	S	0	6	H	Cl	CH_3	CH_2Ph
820	S	1	5	H	H	H	CH_2Ph
821	S	1	5	H	CH_3	H	CH_2Ph
822	S	2	4	H	H	OH	CH_2Ph
823	S	2	4	H	H	H	CH_2Ph
824	S	3	3	H	H	H	CH_2Ph
825	S	3	3	H	H	F	CH_2Ph



No.	X	k	m	X^1	X^2	X^3	R^2
826	O	0	2	H	H	H	CH_2Ph
827	O	0	2	CH_3	H	H	CH_2Ph
828	O	0	3	H	H	H	CH_2Ph
829	O	0	3	OCH_3	H	CH_3	CH_2Ph
830	O	0	4	H	H	H	CH_2Ph
831	O	0	4	Cl	H	H	CH_2Ph
832	O	1	4	H	H	H	CH_2Ph
833	O	1	4	OH	Cl	H	CH_2Ph
834	O	0	5	H	H	H	CH_2Ph
835	O	0	5	H	CH_3	H	CH_2Ph
836	O	2	4	OCH_3	H	OH	CH_2Ph
837	O	2	4	H	H	H	CH_2Ph
838	O	1	5	H	H	H	CH_2Ph
839	O	0	6	H	H	H	CH_2Ph
840	S	0	2	H	H	H	CH_2Ph
841	S	0	2	OCH_3	H	H	CH_2Ph
842	S	0	3	H	H	H	CH_2Ph
843	S	0	3	OCH_3	H	CH_3	CH_2Ph
844	S	0	4	H	H	H	CH_2Ph
845	S	0	4	F	H	H	CH_2Ph
846	S	1	4	H	H	H	CH_2Ph
847	S	1	4	CH_3	Cl	H	CH_2Ph

No.	X	k	m	X^1	X^2	X^3	R^2
848	S	0	5	H	H	H	CH_2Ph
849	S	0	5	H	CH_3	H	CH_2Ph
850	S	2	4	H	H	H	CH_2Ph
851	S	2	4	CH_3	H	H	CH_2Ph
852	S	1	5	H	H	H	CH_2Ph
853	S	0	6	H	H	H	CH_2Ph

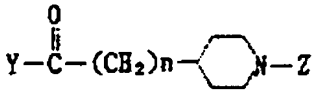
The salt of compound (I) according to the present invention is preferably a physiologically acceptable acid addition salt. The salt mentioned above includes salts with inorganic acids (e.g. hydrochloric acid, phosphoric acid, hydrobromic acid, sulfuric acid) and salts with organic acids (e.g. acetic acid, formic acid, propionic acid, fumaric acid, maleic acid, succinic acid, tartaric acid, citric acid, malic acid, oxalic acid, benzoic acid, methanesulfonic acid, benzenesulfonic acid).

Furthermore, when the compound (I) according to the present invention has an acidic group such as COOH, compound (I) may form a salt with an inorganic base (e.g. sodium, potassium, calcium, magnesium, ammonia) or an organic base (e.g. triethylamine).

The process for producing the compound (I) or its salt of the invention is now described.

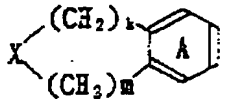
While the following description of the production process applies not only to the production of compound (I) but also to the production of its salt, they may be referred to as the compound (I) below.

The compound (I) can be produced by reacting a compound of the formula (II):



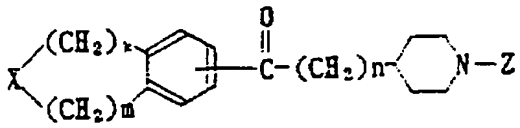
(II)

wherein Y is a halogen; n is as defined in formula (I); Z is an amino-protecting group or a salt thereof with a compound of the formula (III):



(III)

wherein each symbol is as defined in formula (I), or a salt thereof and deprotecting the resulting compound of the formula (IV):



(IV)

wherein each symbol is as defined hereinbefore or a salt thereof.

Y is preferably chloro, bromo or iodo, and a more preferable example of Y is chloro.

Z is preferably acetyl, benzoyl, formyl, methoxycarbonyl, ethoxycarbonyl, t-butoxycarbonyl or benzyloxycarbonyl, and more preferable examples of Z include acetyl and benzoyl.

Here, the compound of formula (II) or a salt thereof can be prepared by processes which are known per

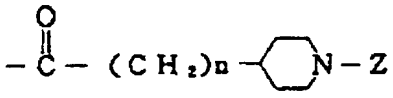
se or processes analogous thereto. For example, it can be produced by the process described in Chemical Pharmaceutical Bulletin, 34, 3747-3761 (1986).

The compound of formula (III) or a salt thereof can be prepared by processes which are known per se or processes analogous thereto. For example, it can be produced by the processes described in Journal of the Organic Chemistry 34, 2235 (1969), Journal of the Organic Chemistry 54, 5574 (1989), Tetrahedron letters 35, 3023 (1977), Bulletin of the Chemical Society of Japan, 56 2300 (1983) and so on.

The salt of compound(I) or compound(IV) according to the present invention is preferably a physiologically acceptable acid addition salt. The salt mentioned above includes salts with inorganic acids (e.g. hydrochloric acid, phosphoric acid, hydrobromic acid, sulfuric acid) and salts with organic acids (e.g. acetic acid, formic acid, propionic acid, fumaric acid, maleic acid, succinic acid, tartaric acid, citric acid, malic acid, oxalic acid, benzoic acid, methanesulfonic acid, benzenesulfonic acid).

The reaction between compound (II) or a salt thereof (e.g. one of the salts mentioned for formula (I)) and compound (III) or a salt thereof can be carried out as follows, for instance. Thus, the compound (II) or a salt thereof is allowed to react with the compound (III) without using a solvent or in a solvent, where necessary in the presence of an acid or the like. The acid may be a Lewis acid (e.g. aluminum chloride, zinc chloride, titanium chloride). The amount of such acid is generally used at a ratio of 1 to 20 moles and preferably 2 to 10 moles relative to one mole of the compound (II). The solvent may be any of the common solvents used in chemical reactions provided it does not interfere with the reaction. For example, dichloromethane, dichloroethane, nitrobenzene, carbon disulfide, etc. can be employed as the solvent. The reaction temperature is generally about -30 °C to 150 °C and preferably about 20 °C to 100 °C. The reaction time is generally 0.5 to 72 hours. The amount of compound (III) or a salt thereof is generally used at a ratio of 1 to 20 moles and preferably about 1 to 5 moles relative to one mole of the compound (II) or a salt thereof.

The position of introduction of the group



of formula (II) into the compound of formula (III) in the above reaction may be any positions of ring A which can be substituted. For example it is predominantly the 6-position when the skeletal structure of compound (III) is 1,2,3,4-tetrahydroquinoline (where ring A is unsubstituted). However, the compounds formed upon introduction into other positions (5-, 7- and 8-positions) may also be produced and isolated.

The compound (IV) or a salt thereof thus produced can be isolated and purified by the conventional procedures such as concentration, pH adjustment, redistribution, solvent extraction, fractional distillation, distillation, crystallization, recrystallization, chromatography and so on. However, the reaction mixture may be directly used as the material to the next reaction stage.

The deprotection of the compound (IV) or a salt thereof can be carried out by treating the compound (IV) or a salt thereof with an acid or a base. Thus, the compound of formula (IV) or a salt thereof is maintained in an aqueous solution of mineral acid (e.g. nitric acid, hydrochloric acid, hydrobromic acid, iodic acid, sulfuric acid) or alkali metal hydroxide (e.g. sodium hydroxide, potassium hydroxide, barium hydroxide, lithium hydroxide) at 10 ° to 150 °C, preferably at 50 ° to 100 °C. Such acid or base is generally used at a ratio of 1 to 100 equivalents and preferably 1 to 40 equivalents relative to the compound (IV) or a salt thereof. The strength of the acid or base is generally about 1 to 10 N, and preferably about 4 to 10 N. The reaction time, which depends on the reaction temperature, is generally 1 to 24 hours and preferably about 2 to 10 hours.

The compound (I) (R^2 = H) or a salt thereof thus produced can be isolated and purified by the conventional procedures such as concentration, pH adjustment, redistribution, solvent extraction, fractional distillation, distillation, crystallization, recrystallization, chromatography and so on. However, the reaction mixture may be directly used as the material to the next reaction stage.

The compound (I) wherein R^2 is a group other than a hydrogen atom or a salt thereof can be produced by reacting a compound (I) (R^2 = H) or a salt thereof with a compound of formula

$R^{2'}$-Y' (V)

wherein $R^{2'}$ is a hydrocarbon group which may be substituted; and Y' is a leaving group.

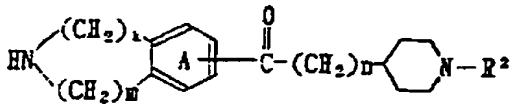
The leaving group Y' includes halogen (e.g. chloro, bromo, iodo), C_{1-6} alkylsulfonyloxy (e.g. methanesulfonyloxy, ethanesulfonyloxy) and C_{6-10} arylsulfonyloxy (e.g. benzenesulfonyloxy, p-toluenesulfonyloxy).

The reaction between the compound (I) (R^2 = H) or a salt thereof and the compound (V) is conducted in a solvent or without using a solvent, where necessary in the presence of a base.

The base mentioned just above includes various inorganic bases such as sodium carbonate, potassium carbonate, lithium carbonate, sodium hydroxide, potassium hydroxide, sodium methoxide, sodium ethoxide, sodium hydride, etc. and various organic bases such as pyridine, 4-dimethylaminopyridine, triethylamine and so on. When a solvent is employed, the solvent includes lower alcohols such as methanol, ethanol,propanol, isopropyl alcohol, n-butanol, t-butanol, etc., ethers such as dioxane, ether, tetrahydrofuran, etc., aromatic hydrocarbons such as toluene, benzene, xylene, etc., amides such as dimethylformamide, dimethylacetamide, hexamethylphosphonotriamide, etc., esters such as ethyl acetate, butyl acetate, etc. which do not interfere with the reaction. This reaction can be conducted under cooling (about 0°C to 10°C), at room temperature (about 10°C to 40°C) or under heating (about 40°C to 120°C), and the reaction time is generally 10 minutes to 48 hours and preferably 2 to 16 hours.

The preferred amount of compound (V) is generally used at a ratio of 0.3 to 5.0 moles relative to one mole of the compound (I) (R^2 = H) or a salt thereof. When a base is employed, the amount of the base is generally used at a ratio of more than one mole and preferably 1.1 to 5 moles relative to one mole of the compound (I) (R^2 = H) or its salt.

If desired, this reaction may be hastened by conducting it in the presence of sodium iodide, potassium iodide, lithium iodide or the like. In such cases, the amount of such iodide is generally used at a ratio of 1 to 5 moles and preferably 1.1 to 1.5 moles relative to one mole of the compound (V). Furthermore, the compound (I) or a salt thereof can also be produced by reacting a compound of the formula (VI):



(VI)

wherein k, m, n, ring A and R^2 are as defined hereinbefore or a salt thereof with a compound of the formula (VII):

$R^{1'}$-Y' (VII)

wherein $R^{1'}$ is a hydrocarbon group which may be substituted or an acyl group which may be substituted; Y' is as defined hereinbefore, under the same conditions as those mentioned for the reaction between the compound (I) (R^2 = H) or a salt thereof and the compound (V). Here, the compound of formula (VI) or a salt thereof can be produced by the processes mentioned above and can be also produced by hydrolyzing the compound (I)($R^2 \neq H$) in which R^1 is acyl or a salt thereof with an acid or a base. This hydrolyzing reaction can be conducted in the same manner as the deprotection of the compound (IV) or a salt thereof.

The compound (I) can also be produced by other known processes or processes analogous thereto (e.g. the compound (I) can be prepared by reduction of the compounds (IV), wherein Z is a carboxylic acid acyl, protection and deprotection of functional groups of the compound (IV) such as ketone may be necessary in the process).

When the compound (I) thus obtained is a free compound, it can be converted to its salt in the per se conventional manner. When the product compound is a salt, it can be converted to the free compound or a different salt by the per se known procedure. The compound (I) or its salt thus obtained can be isolated and purified by the known procedures mentioned hereinbefore.

The compound (I) or its salt according to the present invention has effects on the central nervous system of mammals, has high cholinesterase inhibitory activity, and exhibits potent antiamnesic effects on various amnesia-inducing factors in man and animals (e.g. mice).

The compound (I) or its salt according to the present invention features an excellent separation between effects on the central nervous system and those on the peripheral nervous system, as compared with physostigmine and, at the antiamnesic dose level, does not cause peripheral nervous system effects such as spasm, salivation and diarrhea or, if it does, only minimally. Moreover, it is characterized by a long duration of effects as well as low toxicity and insures a high efficacy when administered orally. The acute toxicity of the compound (I) or its salt according to the present invention is beyond 100 mg/kg.

Therefore, the compound (I) or a salt thereof of the present invention is useful as an agent to improve the brain function for mammalian animals including human beings.

The compound (I) or a salt thereof of the present invention may be used for such diseases as senile dementia, Alzheimer's disease, Huntington's chorea, hyperkinesia and mania, and may be used for the prophylaxis or therapy of these diseases.

The compound (I) or a salt thereof according to the present invention is generally formulated with a pharmaceutically acceptable carrier or excipient and can be administered orally or parenterally to man and other mammalians.

Such pharmaceutical preparations may be those for oral administration (e.g. powders, tablets, granules, capsules, etc.) or for parenteral administration (e.g. suppositories, injections). These preparations can be manufactured by the per se known methods. While the dosage depends on the type of disease and the symptom to be controlled, the usual daily oral dosage per adult human is about 0.01 to 100 mg, preferably 0.1 to 30 mg, and more preferably 0.3 to 10 mg.

The following reference examples, working examples, formulation examples and test examples are intended to illustrate the present invention in further detail and should by no means be construed as defining the metes and bounds of the invention.

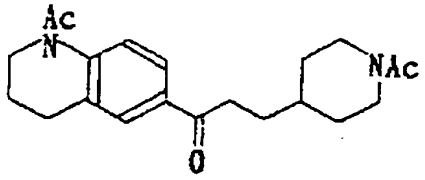
In the examples and reference examples, elution in the procedure of column chromatography was carried out under monitor by TLC (Thin-Layer Chromatography) unless otherwise indicated. TLC monitoring was performed using Merck Kieselgel 60 F_{254} (E. Merck) as the TLC plate, the column elution solvent as the developer and a UV detector for detection. As an adjunctive detection procedure, the spot on the TLC plate was sprayed with 48% HBr, heated to hydrolyze, sprayed with ninhydrin reagent and reheated and the change to a red - reddish purple color was regarded as positive reaction. The fractions containing the object compound were thus identified and pooled. Unless otherwise specified, Merck Kieselgel 60 (70 to 230 mesh (E. Merck)) was used as the silica gel for chromatography.

The term "ambient temperature" or "room temperature" generally means about 5°C to 40°C and the term "atmospheric pressure" means the neighborhood of one atmosphere.

Unless otherwise specified, % denotes percentage by weight.

Reference Example 1

1-Acetyl-6-[3-(1-acetylpiperidin-4-yl)-1-oxopropyl]-1,2,3,4-tetrahydroquinoline



(1) In 300 ml of acetic acid was dissolved 33 g of ethyl β-(pyridin-4-yl)acrylate and catalytic hydrogenation was carried out with platinum oxide as the catalyst under atmospheric pressure at 70 to 80°C. After 40 ml of acetic anhydride was added, the catalyst was filtered off and the solvent was then distilled off under reduced pressure. The residue was dissolved in water and neutralized with potassium carbonate and the reaction product was extracted with dichloromethane. The extract was dried over anhydrous sodium sulfate and the solvent was distilled off to give 44.8 g of an oily compound.

(2) In 200 ml of methanol was dissolved 42.0 g of the above oily compound followed by addition of a solution of 12.7 g of potassium hydroxide in 20 ml of water. The mixture was stirred at 50°C for 1.5 hours and at room temperature for 12 hours. The reaction mixture was neutralized with concentrated hydrochloric acid and the solvent was distilled off. To the residue was added methanol and the insoluble matter was filtered off. The filtrate was concentrated and the resulting crude crystals were collected by filtration to give 27 g of 3-(1-acetylpiperidin-4-yl)propionic acid (m.p. 201 to 206°C).

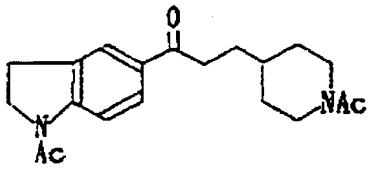
(3) To 20 ml of thionyl chloride was added 3.8 g of 3-(1-acetylpiperidin-4-yl)propionic acid in small portions with ice-cooling and the mixture was stirred for 5 minutes. The excess thionyl chloride was distilled off and 15 g of carbon disulfide and 3.1 g of 1-acetyl-1,2,3,4-tetrahydroquinoline were added to the solid residue followed by gradual addition of 10.7 g of anhydrous aluminum chloride at room temperature. The mixture was refluxed for 2 hours, after which it was poured in ice-water and extracted

with dichloromethane. The extract was dried over anhydrous sodium sulfate and the solvent was distilled off. The residue was purified by chromatography (eluent: ethyl acetate-methanol = 40:1 (v/v)) to give 1.4 g of a colorless oil.

Elemental analysis, for $C_{21}H_{28}N_2O_3$			
Calcd.:	C, 70.76;	H, 7.92;	N, 7.86
Found :	C, 70.68;	H, 7.80;	N, 7.64

Reference Example 2

1-Acetyl-6-[3-(1-acetylpiperidin-4-yl)-1-oxopropyl]-1,2,3,4-tetrahydroquinoline (A) and 1-acetyl-7-[3-(1-acetylpiperidin-4-yl)-1-oxopropyl]-1,2,3,4-tetrahydroquinoline (B)



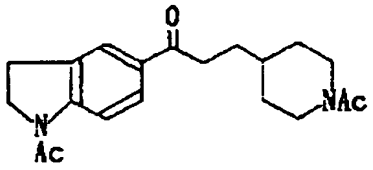
(1) To 100 ml of thionyl chloride was added 26 g of 3-(1-acetylpiperidin-4-yl)propionic acid, obtained in Reference Example 1-(2), in small portions with ice-cooling. The mixture was stirred for 5 minutes, after which the excess thionyl chloride was distilled off and the solid residue was washed with diethyl ether to give 26.4 g of 3-(1-acetylpiperidin-4-yl)propionyl chloride as a pale yellow powder.

(2) To a mixture of 42.5 g of 1-acetyl-1,2,3,4-tetrahydroquinoline and 30 ml of carbon disulfide was added 71 g of anhydrous aluminum chloride followed by addition of 26.4 g of 3-(1-acetylpiperidin-4-yl)-propionyl chloride at room temperature. The mixture was stirred at room temperature for 16 hours, after which it was treated in the same manner as Reference Example 1-(3) to give 25 g of a mixture of 1-acetyl-6-[3-(1-acetylpiperidin-4-yl)-1-oxopropyl]-1,2,3,4-tetrahydroquinoline (A) and 1-acetyl-7-[3-(1-acetylpiperidin-4-yl)-1-oxopropyl]-1,2,3,4-tetrahydroquinoline (B) as a pale yellow oil.

Elemental analysis, for $C_{21}H_{28}N_2O_3$			
Calcd.:	C, 70.76;	H, 7.92;	N, 7.86
Found :	C, 70.81;	H, 7.69;	N, 7.83

Reference Example 3

1-Acetyl-5-[3-(1-acetylpiperidin-4-yl)-1-oxopropyl]-2,3-dihydro-1H-indole

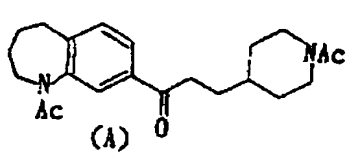


Using 24 g of 1-acetyl-2,3-dihydro-1H-indole, the procedure of Reference Example 2-(2) was followed to give a solid. This solid was recrystallized from dichloromethane-diethyl ether to give 26 g of colorless crystals melting at 148 to 149 °C.

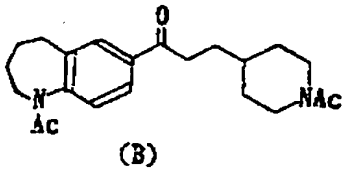
Elemental analysis, for $C_{20}H_{26}N_2O_3$			
Calcd.:	C, 70.15;	H, 7.65;	N, 8.18
Found :	C, 69.97;	H, 7.71;	N, 7.98

Reference Example 4

1-Acetyl-8-[3-(1-acetylpiperidin-4-yl)-1-oxopropyl]-2,3,4,5-tetrahydro-1H-1-benzazepine (A) and 1-acetyl-7-[3-(1-acetylpiperidin-4-yl)-1-oxopropyl]-2,3,4,5-tetrahydro-1H-1-benzazepine (B)



(A)



(B)

Using 8.7 g of 1-acetyl-2,3,4,5-tetrahydro-1H-1-benzazepine, the procedure of Reference Example 2-(2) was followed to give a solid, which was then recrystallized from dichloromethane-diethyl ether to give 6.5 g of title compound A as colorless crystals melting at 133 to 134°C.

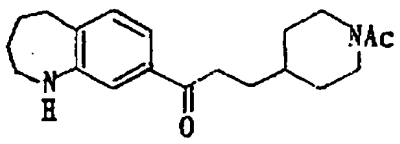
Elemental analysis, for $C_{22}H_{30}N_2O_3$			
Calcd.:	C, 71.32;	H, 8.16;	N, 7.56
Found :	C, 71.10;	H, 8.21;	N, 7.61

The recrystallization mother liquor was purified by column chromatography (eluent: ethyl acetate: methanol = 100:1) to recover 0.3 g of title compound B as a pale yellow oil.

Elemental analysis, for $C_{22}H_{30}N_2O_3$			
Calcd.:	C, 71.32;	H, 8.16;	N, 7.56
Found :	C, 71.13;	H, 8.04;	N, 7.43

Reference Example 5

8-[3-(1-Acetylpiperidin-4-yl)-1-oxopropyl]-2,3,4,5-tetrahydro-1H-1-benzazepine

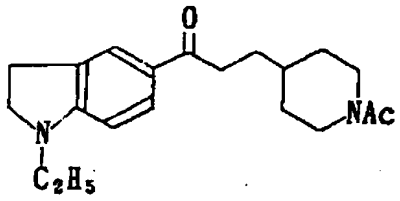


Using 2.2 g of the compound obtained in Example 17, the procedure of Example 7-(1) was followed to give 2.15 g of colorless crystals melting at 86 to 88°C.

Elemental analysis, for $C_{20}H_{28}N_2O_2$			
Calcd.:	C, 73.14;	H, 8.59;	N, 8.53
Found :	C, 72.91;	H, 8.38;	N, 8.47

Reference Example 6

5-[3-(1-Acetylpiperidin-4-yl)-1-oxopropyl]-1-ethyl-2,3-dihydro-1H-indole

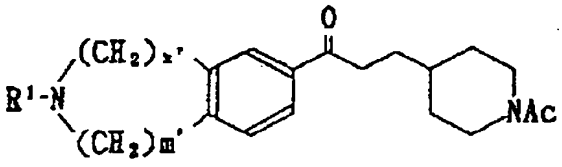


In 10 ml of ethanol were dissolved 0.8 g of 5-[3-(1-acetylpiperidin-4-yl)-1-oxopropyl]-2,3-dihydro-1H-indole, 2.1 g of ethyl iodide and 0.5 g of potassium carbonate and the solution was refluxed for 24 hours. The solid matter and the solvent were removed and the residue was purified by column chromatography (eluent: ethyl acetate: methanol = 20:1) to give 0.85 g of the title compound as a pale yellow oil.

Elemental analysis, for $C_{20}H_{28}N_2O_2$			
Calcd.:	C, 73.14;	H, 8.59;	N, 8.53
Found :	C, 73.03;	H, 8.54;	N, 8.56

Reference Example 7

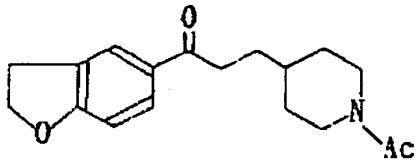
Using the compound obtained in Example 14-(1) or Reference Example 5, the procedure of Reference Example 7 was followed to give the compounds as oil as follows.



Compound No.	k'	m'	R^1	Molecular formula	Analysis Calcd. (Found)		
					C	H	N
1	2	0	C_3H_7	$C_{21}H_{30}N_2O_2$	73.65 (73.46	8.83 8.85	8.18 7.99)
2	2	0	C_4H_9	$C_{22}H_{32}N_2O_2$	74.12 (74.03	9.05 9.02	7.86 7.61)
3	2	0	C_5H_{11}	$C_{23}H_{34}N_2O_2$	74.56 (74.51	9.25 9.09	7.56 7.45)
4	2	0	CH_2CH_2Ph	$C_{25}H_{32}N_2O_2$	77.19 (77.12	7.97 8.02	6.93 6.86)
5	0	4	CH_3	$C_{21}H_{30}N_2O_2$	73.65 (73.55	8.83 8.73	8.18 8.16)
6	0	4	C_2H_5	$C_{22}H_{32}N_2O_2$	74.12 (74.01	9.05 8.96	7.86 7.75)
7	0	4	C_3H_7	$C_{23}H_{34}N_2O_2$	74.56 (74.37	9.25 9.11	7.56 7.43)

Reference Example 8

5-[3-(1-Acetylpiperidin-4-yl)-1-oxopropyl]-2,3-dihydrobenzofuran

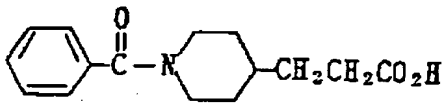


To 200 ml of 1,2-dichloroethane were added 9.65 g (44 mmol) of 3-(1-acetylpiperidin-4-yl)propionic acid chloride and 10.65 g (89 mmol) of 2,3-dihydrobenzofuran. To the mixture was added 12.82 g (96 mmol) of aluminum chloride in limited amounts, then the mixture was stirred for 3 hours at room temperature. The reaction mixture was poured into ice-water, which was subjected to extraction with methylene chloride. Organic layers were combined and washed with water and dried over anhydrous sodium sulfate, followed by distilling off the solvent. The residue was purified by means of a silica gel column chromatography (ethyl acetate) to give 10.47 g (78%) of 5-[3-(1-acetylpiperidin-4-yl)-1-oxopropyl]-2,3-dihdyrobenzofuran. Recrystallization from methylene chloride - diethyl ether gave colorless needles, m.p. 93-95 °C.

Elemental Analysis for $C_{18}H_{23}NO_3$:			
Calcd.:	C, 71.73;	H, 7.69;	N, 4.65.
Found :	C, 71.57;	H, 7.77;	N, 4.58

Reference Example 9

3-(1-Benzoylpiperidin-4-yl)propionic acid

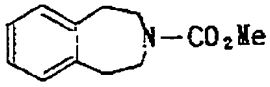


(1) In 100 ml of acetic acid was dissolved 12 g of ethyl β-(pyridin-4-yl)acrylate and catalytic reduction was carried out with 1 g of platinum oxide as the catalyst under atmospheric pressure at 70-80 °C. The catalyst was filtered off and the solvent was distilled off under reduced pressure, then the residue was dissolved in 100 ml of dioxane. To the dioxane solution was added 100 ml of an aqueous solution of 12 g of sodium hydrogen carbonate, and the mixture was stirred for 20 minutes at room temperature. To the resultant mixture was added dropwise 8 ml of benzoyl chloride at room temperatures, and the mixture was stirred for two hours. The reaction product was extracted with dichloromethane. The extract was dried over anhydrous sodium sulfate and the solvent was distilled off to give 17.5 g of ethyl 3-(1-benzoylpiperidin-4-yl) propionate as an pale yellow oily product.
(2) Using 17 g of the compound obtained in (1), the procedure of Example 1-(2) was followed to give 15 g of the the above-titled compound as colorless crystals, m.p. 153-155 °C.

Elemental Analysis for $C_{15}H_{19}NO_3$:			
Calcd.:	C, 68.94;	H, 7.33;	N, 5.36
Found :	C, 68.71;	H, 7.44;	N, 5.20

Reference Example 10

3-Methoxycarbonyl-2,3,4,5-tetrahydro-1H-3-benzazepine

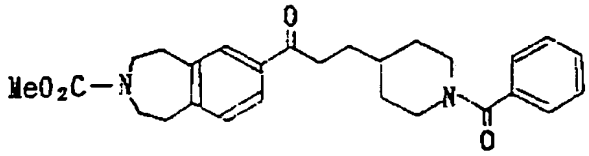


In 150 ml of water was dissolved 4.13 g (0.10 mol.) of sodium hydroxide. To the solution was added 15.27 g (10.4 mmol.) of 2,3,4,5-tetrahydro-1H-3-benzazepine. The reaction mixture was cooled with ice, and there was added dropwise 7.9 ml (0.10 mol.) of methyl chloroformate. The mixture was stirred for 2.5 hours at room temperature, then extracted with dichloromethane. The extract was dried over anhydrous sodium sulfate and the solvent was distilled off to leave 20.46 g (98%) of 3-methoxycarbonyl-2,3,4,5-tetrahydro-1H-3-benzazepine as colorless crystals. Recrystallization from diethyl ether - n-hexane gave colorless needles, m.p. 53-54 °C.

Elemental Analysis for $C_{12}H_{15}NO_2$:			
Calcd.:	C, 70.22;	H, 7.37;	N, 6.82
Found :	C, 70.02;	H, 7.41;	N, 6.68

Reference Example 11

3-Methoxycarbonyl-7-[3-(1-benzoylpiperidin-4-yl)-1-oxopropyl]-2,3,4,5-tetrahydro-1H-3-benzazepine

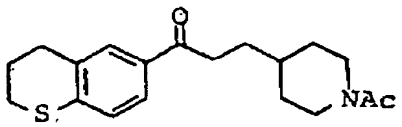


Under ice-cooling, 1.5 ml of thionyl chloride was added dropwise to 1.08 g (4.1 mmol.) of 3-(1-benzoylpiperidin-4-yl)propionic acid obtained in Reference Example 9. The mixture was stirred for 40 minutes at 0° C, then thionyl chloride was distilled off. The residue was dissolved in 20 ml of 1,2-dichloroethane, to which was added 0.81 g (3.9 mmol.) of 3-methoxycarbonyl-2,3,4,5-tetrahydro-1H-3-benzazepine obtained in Reference Example 10. To the mixture was added 1.75 g (13.1 mmol.) of aluminum chloride in small portions. The mixture was stirred for one hour at room temperature, then the reaction mixture was poured into ice-water and extracted with dichloromethane. The organic layers were combined and washed with water once, then dried over anhydrous sodium sulfate, followed by distilling off the solvent. Purification by means of a silica gel column chromatography gave 1.46 g (83%) of 3-methoxycarbonyl-7-[3-(1-benzoylpiperidin-4-yl)-1-oxopropyl]-2,3,4,5-tetrahydro-1H-3-benzazepine. Recrystallization from ethyl acetate - n-hexane gave colorless needles, m.p. 120-123° C.

Elemental Analysis for $C_{27}H_{32}N_2O_4$:			
Calcd.:	C, 72.30;	H, 7.19;	N, 6.25
Found :	C, 71.99;	H, 7.22;	N, 6.12

Reference Example 12

6-[3-(1-Acetylpiperidin-4-yl)-1-oxopropyl]-3,4-dihydro-2H-1-benzothiopyran

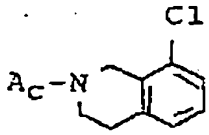


To a mixture of 3,4-dihydro-2H-1-benzothiopyran (1.5g) and 3-(1-acetylpiperidin-4-yl)propionyl chloride (2.18g) in 1,2-dichloroethane (20ml) was added aluminum chloride (3.2g) portionwise at 10-15° C. The mixture was stirred at room temperature for 2 hours then refluxed for additional 2 hours, and poured into ice-water. The mixture was extracted with dichloromethane, washed with water, dried over anhydrous sodium sulfate. The solvent was distilled off. The residue was purified by silica gel column chromatography (developing solvent: ethyl acetate) to obtain 2.7g of the title compound as a pale yellow oil.

Elemental analysis, for $C_{19}H_{25}NO_2S$			
Calcd.:	C, 68.85;	H, 7.60;	N, 4.23
Found :	C, 68.66;	H, 7.82;	N. 4.13

Reference Example 13

2-Acetyl-8-chloro-1,2,3,4-tetrahydoisoquinoline

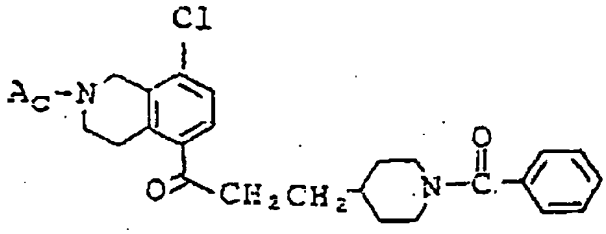


To a mixture of 28.6 g of 8-chloro-1,2,3,4-tetrahydoisoquinoline hydrochloride in 140 ml of dichloromethane was added 140 ml of 1N aqueous NaOH solution and 17.6 g of $NaHCO_3$. To the solution was added dropwise 14.5 ml of acetic anhydride at 5°C. The mixture was stirred at room temperature for 1 hour. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic extracts were washed with water, dried over anhydrous sodicum sulfate. The solvent was distilled off to give 29.1 g of the title compound as a pale red oil.

Elemental analysis, for $C_{11}H_{12}ClNO$:			
Calcd.:	C, 63.01;	H, 5.77;	N, 6.68.
Found :	C, 62.82;	H, 5.86;	N, 6.56.

Reference Example 14

2-Acetyl-5-[3-(1-benzoylpiperidin-4-yl)-1-oxopropyl]-8-chloro-1,2,3,4-tetrahydroisoquinoline

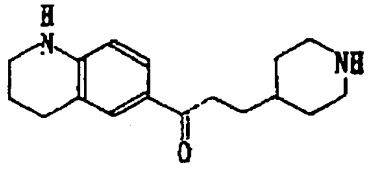


Using 21.0 g of the compound obtained in Reference Example 13, the procedure of Reference Example 11 was followed to give 9.2 g of the title compound as a pale yellow oil.

Elemental analysis, for $C_{26}H_{29}ClN_2O_3$:			
Calcd.:	C, 68.94;	H, 6.45;	N, 6.18.
Found :	C, 68.83;	H, 6.52;	N, 6.04.

Example 1

6-[1-Oxo-3-(piperidin-4-yl)propyl]-1,2,3,4-tetrahydroquinoline

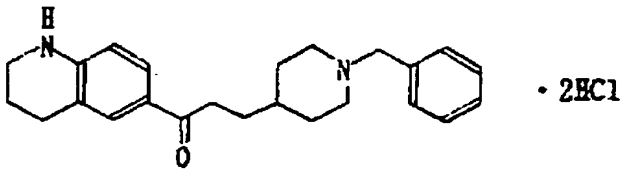


A mixture of 1.3 g of 1-acetyl-6-[3-(1-acetylpiperidin-4-yl)-1-oxopropyl]-1,2,3,4-tetrahydroquinoline obtained in Reference Example 1 and 20 ml of concentrated hydrochloric acid was refluxed for 16 hours. The reaction mixture was then concentrated and the residue was dissolved in water. This solution was washed with ether and the aqueous layer was adjusted to pH about 10 with 10% sodium hydroxide solution and extracted with dichloromethane. The extract was dried over anhydrous sodium sulfate and the solvent was distilled off under reduced pressure to give 0.9 g of a colorless oil.

Elemental analysis, for $C_{17}H_{24}N_2O$			
Calcd.:	C, 74.96;	H, 8.88;	N, 10.29
Found :	C, 74.87;	H, 8.68;	N, 10.30

Example 2

6-[1-Oxo-3-[1-(phenylmethyl)piperidin-4-yl]propyl]-1,2,3,4-tetrahydroquinoline dihydrochloride

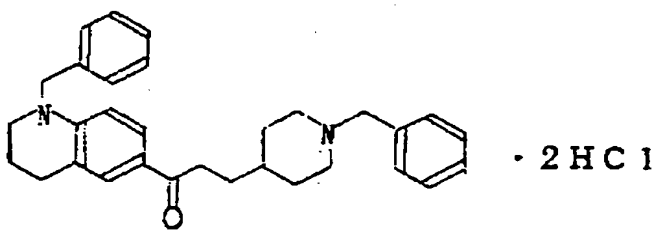


To a mixture of 1.3 g of 6-[1-oxo-3-(piperidin-4-yl)propyl]-1,2,3,4-tetrahydroquinoline, 0.9 g of potassium carbonate and 10 ml of ethanol was added dropwise 2 ml of an ethanolic solution of 0.74 g of benzyl bromide with ice-cooling. The mixture was stirred at room temperature for 2 hours and the solid matter and the solvent were removed. The residue was subjected to column chromatography (eluent; ethyl acetate: methanol = 20:1 (v/v)) and the eluate containing the desired compound was distilled to remove the solvent. The residue was treated with 2.4 ml of 4N methanolic hydrochloride to give a solid. This solid was recrystallized from methanol-ether to give 1.55 g of a colorless powder melting at 110 to 125°C (decomp.)

Elemental analysis, for $C_{24}H_{30}N_2O \cdot 2HCl$			
Calcd.:	C, 66.20;	H, 7.41;	N, 6.43
Found :	C, 66.00;	H, 7.35;	N, 6.22

Example 3

1-(Phenylmethyl)-6-[3-[1-(phenylmethyl)piperidin-4-yl]-1-oxopropyl]-1,2,3,4-tetrahydroquinoline dihydrochloride



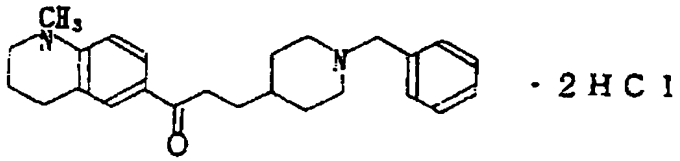
To 5 ml of a solution of 0.5 g of 6-[1-oxo-3-[1-(phenylmethyl)piperidin-4-yl]propyl]-1,2,3,4-

tetrahydroquinoline (free base) according to Example 2 in N,N-dimethylformamide was gradually added 40 mg of sodium hydride (oil-free) and the mixture was stirred at room temperature for 1 hour. To this solution was added dropwise 0.22 g of benzyl bromide with ice-cooling and the mixture was stirred at room temperature for 6 hours. The reaction mixture was then treated as in Example 2 and the residue was purified by column chromatography (eluent; ethyl acetate: methanol = 20:1 (v/v)). The eluate containing the desired compound was distilled under reduced pressure to remove the solvent and the resulting oil was treated with 0.7 ml of 4N-methanolic hydrochloric acid to give a solid. This solid was recrystallized from ethanol-ether to give 0.28 g of colorless crystals melting at 112 to 117°C (decomp.).

Elemental analysis, for $C_{31}H_{36}N_2O \cdot 2HCl$			
Calcd.:	C, 70.85;	H, 7.29;	N, 5.33
Found :	C, 70.81;	H, 7.12;	N, 5.18

Example 4

1-Methyl-6-[3-[1-(phenylmethyl)piperidin-4-yl]-1-oxopropyl]-1,2,3,4-tetrahydroquinoline dihydrochloride

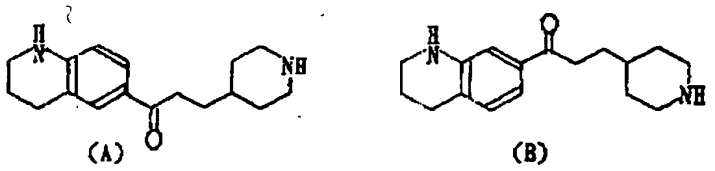


To 3 ml of a solution of 0.2 g of 6-[3-[1-(phenylmethyl)piperidin-4-yl]-1-oxopropyl]-1,2,3,4-tetrahydroquinoline dihydrochloride obtained according to Example 2 in N,N-dimethylformamide was gradually added 37 mg of sodium hydride (oil-free). The mixture was stirred at room temperature for 1 hour, after which 62 mg of methyl iodide was added. The mixture was stirred at room temperature for 6 hours, at the end of which time 15 mg of sodium hydride (oil-fee) and 40 ml of ethyl chlorocarbonate were added in that order. The mixture was stirred for 1 hour and then poured in ice-water and extracted with dichloromethane. The extract was dried over anhydrous sodium sulfate and the solvent was distilled off under reduced pressure. The residue was subjected to column chromatography (eluent; ethyl acetate:methanol = 20:1 (v/v)) and the eluate containing the desired compound was distilled under reduced pressure to remove the solvent. The resulting oil was treated with 0.23 ml of 4N-methanolic hydrochloric acid to give 0.1 g of an amorphous powder.

Elemental analysis, for $C_{25}H_{32}N_2O \cdot 2HCl$			
Calcd.:	C, 66.81;	H, 7.62;	N, 6.23
Found :	C, 66.83;	H, 7.55;	N, 6.09

Example 5

6-[1-Oxo-3-(piperidin-4-yl)propyl]-1,2,3,4-tetrahydroquinoline (A) and 7-[1-oxo-3-(piperidin-4-yl)propyl]-1,2,3,4-tetrahydroquinoline (B)



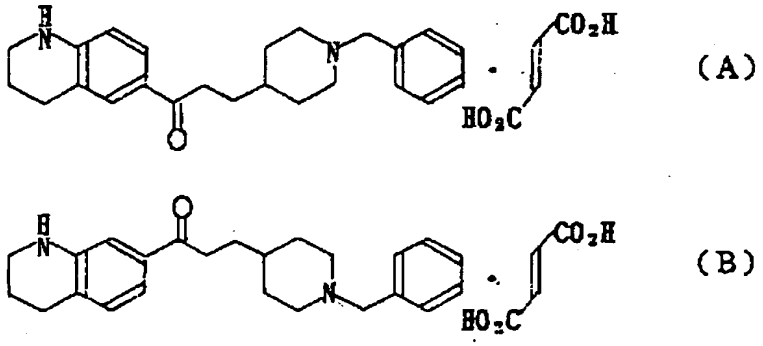
(A) (B)

Using 23 g of the compound obtained according to Reference Example 2, the procedure of Example 1 was followed to give 16.9 g of a mixture of 6-[1-oxo-3-(piperidin-4-yl)propyl]-1,2,3,4-tetrahydroquinoline (A) and 7-[1-oxo-3-(piperidin-4-yl)-propyl]-1,2,3,4-tetrahydroquinoline (B) as a pale yellow oil.

Elemental analysis, for $C_{17}H_{24}N_2O$			
Calcd.:	C, 74.96;	H, 7.88;	N, 10.29
Found :	C, 74.69;	H, 8.90;	N, 10.22

Example 6

6-[1-Oxo-3-[1-(phenylmethyl)piperidin-4-yl]propyl]-1,2,3,4-tetrahydroquinoline fumarate (A) and 7-[1-Oxo-3-[1-(phenylmethyl)piperidin-4-yl]propyl]-1,2,3,4-tetrahydroquinoline fumarate (B)



(A)

(B)

Using 1.8 g of the compound obtained in Example 5, the procedure of Example 2 was followed to give 1.82 g of the free base of the title compound mixture A and B. The first crop of crystals (0.65 g) from a solution of this mixture in diethyl ether, i.e. 7-[1-oxo-3-[1-(phenylmethyl)piperidin-4-yl]propyl]-1,2,3,4-tetrahydroquinoline (m.p. 132-135°c), was treated with an equivalent of fumaric acid to give 0.69 g of the title fumarate (B) as colorless crystals melting at 175 to 177°C (decomp.).

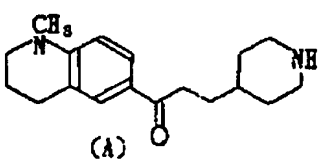
Elemental analysis, for $C_{24}H_{30}N_2O \cdot C_4H_4O_4$			
Calcd.:	C, 70.27;	H, 7.16;	N, 5.85
Found :	C, 70.01;	H, 6.97;	N, 5.98

The mother liquor of said diethyl ether solution was also concentrated to recover 0.7 g of 6-[1-oxo-3-[1-(phenylmethyl)piperidin-4-yl]propyl]-1,2,3,4-tetrahydroquinoline as crystals (m.p. 126 to 129°C). This crop of crystals was treated with an equivalent of fumaric acid to give 0.78 g of the title fumarate (A) as colorless crystals melting at 138 to 142°C (decomp.)

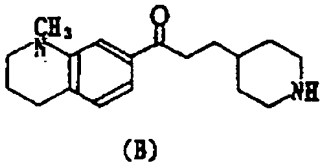
Elemental analysis, for $C_{24}H_{30}N_2O \cdot C_4H_4O_4$			
Calcd.:	C, 70.27;	H, 7.16;	N, 5.85
Found :	C, 70.13;	H, 7.13;	N, 5.77

Example 7

1-Methyl-6-[1-oxo-3-(piperidin-4-yl)propyl]-1,2,3,4-tetrahydroquinoline (A) and 1-methyl-7-[1-oxo-3-(piperidin-4-yl)propyl]-1,2,3,4-tetrahydroquinoline (B)



(A)



(B)

(1) To 40 ml of a solution of 14.2 g of the compound obtained according to Example 5 in dichloromethane was added dropwise 10 ml of a solution of 5.1 g of acetic anhydride in dichloromethane with ice-cooling. The mixture was then stirred at room temperature for 10 minutes, after which it was washed with 10% sodium hydroxide solution and dried over anhydrous sodium sulfate. Finally the solvent was distilled off to give 14.9 g of a mixture of 6-[1-oxo-3-(1-acetylpiperidin-4-yl)propyl]-1,2,3,4-tetrahydroquinoline and 7-[1-oxo-3-(1-acetylpiperidin-4-yl)propyl]-1,2,3,4-tetrahydroquinoline as a colorless oil.

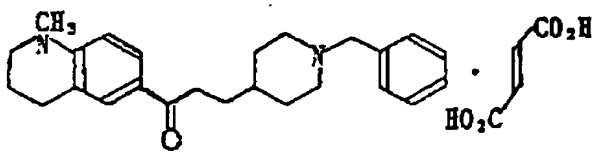
(2) A mixture of 7.1 g of the oil obtained in (1) and 1.6 g of trimethyl phosphate was heated at 190° C for 2 hours. After cooling to room temperature, 20 ml of dichloromethane as well as aqueous sodium hydroxide solution ($NaOH/H_2O$ = 1.74 g/11 ml) was added and the mixture was refluxed for 2 hours. The dichloromethane layer was washed with water and dried over anhydrous sodium sulfate and the solvent was distilled off. The residue was purified by column chromatography (eluent; ethyl acetate: methanol = 30:1) to give 5.5 g of a mixture of 6-[3-(1-acetylpiperidin-4-yl)-1-oxopropyl]-1-methyl-1,2,3,4-tetrahydroquinoline and 7-[3-(1-acetylpiperidin-4-yl)-1-oxopropyl]-1-methyl-1,2,3,4-tetrahydroquinoline as a pale yellow oil.

(3) Using 3.9 g of the oil obtained in (2), the procedure of Example 1 was followed to give 3.2 g of a mixture of the title compounds as a pale yellow oil.

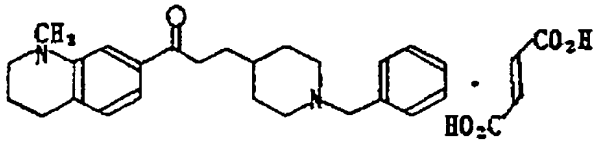
Elemental analysis, for $C_{18}H_{26}N_2O$			
Calcd.:	C, 75.48;	H, 9.15;	N, 9.78
Found :	C, 75.21;	H, 9.06;	N, 9.82

Example 8

1-Methyl-6-[1-oxo-3-[1-(phenylmethyl)piperidin-4-yl]-propyl]-1,2,3,4-tetrahydroquinoline fumarate (A) and 1-methyl-7-[1-oxo-3-[1-(phenylmethyl)piperidin-4-yl]propyl]-1,2,3,4-tetrahydroquinoline fumarate (B)



(A)



(B)

Using 3.1 g of the compound obtained in Example 7, the procedure of Example 2 was followed to give 3.8 g of the free base of the mixture of title compounds A and B. This mixture was purified by chromatography (eluent; ethyl acetate: methanol = 50:1) to give 1.6 g of 1-methyl-6-[1oxo-3-[1-(phenylmethyl)piperidin-4-yl]propyl]-1,2,3,4-tetrahydroquinoline (colorless oil) and 1.7 g of 1methyl-7-[1-oxo-3-[1-(phenylmethyl)piperidin-4-yl]propyl]-1,2,3,4-tetrahydroquinoline (colorless oil).

Then, 1.6 g of 1-methyl-6-[1-oxo-3-[1-(phenylmethyl)piperidin-4-yl]propyl]-1,2,3,4-tetrahydroquinoline was treated with an equivalent of fumaric acid to give 1.7 g of the title fumarate (A) as colorless crystals melting at 170 to 172°C (decomp.)

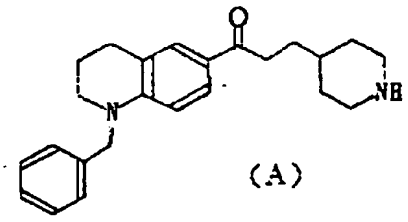
Elemental analysis, for $C_{25}H_{32}N_2O \cdot C_4H_4O_4$			
Calcd.:	C, 70.71;	H, 7.37;	N, 5.69
Found :	C, 70.61;	H, 7.24;	N, 5.63

On the other hand, 1.7 g of 1-methyl-7-[1-oxo-3-[1-(phenylmethyl)piperidin-4-yl]propyl]-1,2,3,4-tetrahydroquinoline was treated with an equivalent of fumaric acid to give 1.65g of the title fumarate (B) as colorless crystals melting at 143 to 144°C (decomp.)

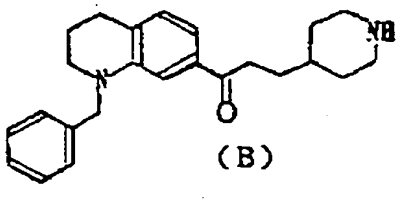
Elemental analysis, for $C_{25}H_{32}N_2O \cdot C_4H_4O_4$			
Calcd.:	C, 70.71;	H, 7.37;	N, 5.69
Found :	C, 70.54;	H, 7.09;	N, 5.77

Example 9

1-(Phenylmethyl)-6-[1-oxo-3-(piperidin-4-yl)propyl]-1,2,3,4-tetrahydroquinoline (A) and 1-(phenylmethyl)-7-[1-oxo-3-(piperidin-4-yl)propyl]-1,2,3,4-tetrahydroquinoline (B)



(A)



(B)

(1) To a mixture of 5.2 g of the compound obtained according to Example 7-(1), 3.0 g of potassium carbonate and 30 ml of ethanol was added dropwise 5 ml of an ethanolic solution of 2.7 g of benzyl

bromide with ice-cooling. The mixture was stirred at room temperature for 2 hours and the solid matter and the solvent were removed. The residue was subjected to chromatography (eluent; ethyl acetate: methanol = 20:1 (v/v)) to give 3.2 g of 7-[3-(1-acetylpiperidin-4-yl)-1-oxopropyl]-1-(phenylmethyl)-1,2,3,4tetrahydroquinoline (a colorless oil) and 1.8 g of 6-[3-(1-acetylpiperidin-4-yl)-1-oxopropyl]-1,2,3,4-tetrahydroquinoline.

(2) A mixture of 1.8 g of 6-[3-(1-acetylpiperidin-4-yl)-1-oxopropyl]-1,2,3,4-tetrahydroquinoline recovered in (1), 1.03 g of potassium carbonate, 1.96 g of benzyl bromide and 20 ml of ethanol was refluxed for 5 hours and the solid matter and the solvent were removed. The residue was subjected to chromatography (eluent; ethyl acetate: methanol = 20:1) to give 2.1 g of 6-[3-(1-acetylpiperidin-4-yl)-1-oxopropyl]-1-(phenylmethyl)-1,2,3,4-tetrahydroquinoline as a colorless oil.

(3) Using 3.15 g of 7-[3-(1-acetylpiperidin-4-yl)-1-oxopropyl]-1-(phenylmethyl)-1,2,3,4-tetrahydroquinoline obtained in (1), the procedure of Example 1 was followed to give 2.8 g of 1-(phenylmethyl)-7-[1-oxo-3-(piperidin-4-yl)propyl]-1,2,3,4-tetrahydroquinoline (B) as a pale yellow oil.

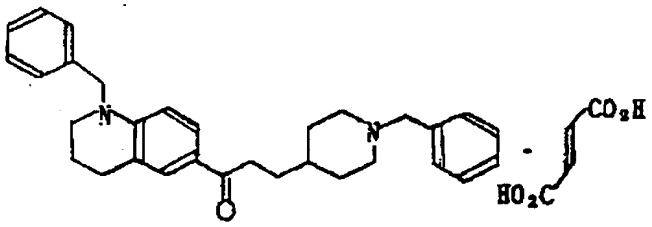
Elemental analysis, for $C_{24}H_{30}N_2O$			
Calcd.:	C, 79.52;	H, 8.34;	N, 7.73
Found :	C, 79.28;	H, 8.21;	N, 7.59

(4) Using 1.9 g of 6-[3-(1-acetylpiperidin-4-yl)-1-oxopropyl]-1-(phenylmethyl)-1,2,3,4-tetrahydroquinoline obtained in (2), the procedure of Example 1 was followed to give 1.63 g of 1-(phenylmethyl)-6-[1-oxo-3-(piperidin-4-yl)propyl]-1,2,3,4-tetrahydroquinoline (A) as a pale yellow oil.

Elemental analysis, for $C_{24}H_{30}N_2O$			
Calcd.:	C, 79.52;	H, 8.34;	N, 7.73
Found :	C, 79.43;	H, 8.16;	N, 7.48

Example 10

1-(Phenylmethyl)-6-[1-oxo-3-[1-(phenylmethyl)piperidin-4-yl]propyl]-1,2,3,4-tetrahydroquinoline fumarate

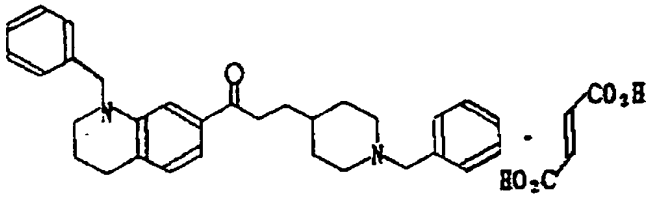


Using 1.5 g of the compound obtained in Example 9-(4), the procedure of Example 2 was followed to give 1.6 g of 1-(phenylmethyl)-6-[1-oxo-3-[1-(phenylmethyl)piperidin-4-yl]propyl]-1,2,3,4-tetrahydroquinoline (free base) as a colorless oil. This oil (1.6 g) was treated with an equivalent of fumaric acid to give 1.7 g of the title fumarate as colorless crystals melting at 178 to 181 °C (decomp.)

Elemental analysis, for $C_{31}H_{36}N_2O \cdot C_4H_4O_4$			
Calcd.:	C, 73.92;	H, 7.09;	N, 4.93
Found :	C, 73.64;	H, 7.22;	N, 4.84

Example 11

1-(Phenylmethyl)-7-[1-oxo-3-[1-(phenylmethyl)piperidin-4-yl]propyl]-1,2,3,4-tetrahydroquinoline fumarate

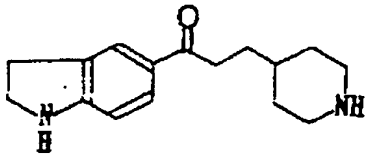


Using 2.75 g of the compound obtained in Example 9-(3), the procedure of Example 2 was followed to give 2.95 g of 1-(phenylmethyl)-7-[1-oxo-3-[1-(phenylmethyl)piperidin-4-yl]propyl]-1,2,3,4-tetrahydroquinoline (free base) as a colorless oil. This oil (2.95 g) was treated with an equivalent of fumaric acid to give 3.1 g of the title fumarate as colorless crystals melting at 180 to 182 °C (decomp.).

Elemental analysis, for $C_{31}H_{36}N_2O \cdot C_4H_4O_4$			
Calcd.:	C, 73.92;	H, 7.09;	N, 4.93
Found :	C, 73.72;	H, 7.02;	N, 4.86

Example 12

2,3-Dihydro-5-[1-oxo-3-(piperidin-4-yl)propyl]-1H-indole

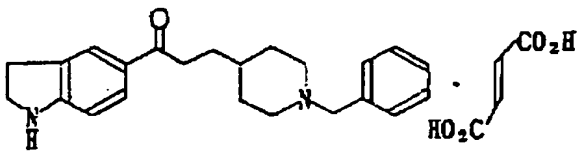


Using 10 g of the compound obtained in Reference Example 3, the procedure of Example 1 was followed and the resulting solid product was recrystallized from dichloromethane - diethyl ether to give 7.08 g of pale yellow crystals melting at 137 to 139 °C.

Elemental analysis, for $C_{16}H_{22}N_2O$			
Calcd.:	C, 74.38;	H, 8.58;	N, 10.84
Found :	C, 74.11;	H, 8.75;	N, 10.67

Example 13

2,3-Dihydro-5-[1-oxo-3-[1-(phenylmethyl)piperidin-4-yl]propyl]-1H-indole fumarate

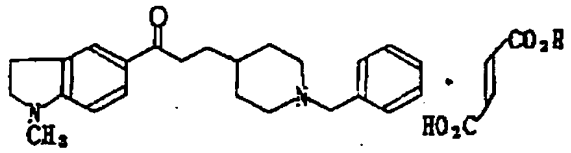


Using 2 g of the compound obtained in Example 12, the procedure of Example 2 was followed to give 2.3 g of the free base of the title compound as colorless crystals melting at 81 to 82 °C. The crystals (2.3 g) were then treated with an equivalent of fumaric acid to give 2.6 g of the title fumarate as colorless crystals melting at 150 to 153 °C (decomp.).

Elemental analysis, for $C_{23}H_{28}N_2O \cdot C_4H_4O_4$			
Calcd.:	C, 69.81;	H, 6.94;	N, 6.03
Found :	C, 69.68;	H, 6.71;	N, 5.93

Example 14

2,3-Dihydro-1-methyl-5-[1-oxo-3-[1-(phenylmethyl)piperidin-4-yl)propyl]-1H-indole fumarate



(1) Using 3 g of the compound obtained in Example 12, the procedure of Example 7-(1) was followed to give 3.1 g of 5-[3-(1-acetylpiperidin-4-yl)-1-oxopropyl]-2,3-dihydro-1H-indole as colorless crystals melting at 145 to 146 °C.

Elemental analysis, for $C_{18}H_{24}N_2O_2$			
Calcd.:	C, 71.97;	H, 8.05;	N, 9.33
Found :	C, 71.92;	H, 7.94;	N, 9.11

(2) Using 1.5 g of the compound prepared in (1), the procedure of Example 7-(2) was followed to give 1.25 g of 5-[3-(1-acetylpiperidin-4-yl)-1-oxopropyl]-2,3-dihydro-1-methyl-1H-indole as a colorless oil.
(3) Using 1.0 g of the compound obtained in (2), the procedure of Example 1 was followed to give 0.83 g of 2,3-dihydro-1-methyl-5-[1-oxo-3-(piperidin-4-yl)propyl-1Hindole as a pale yellow oil.

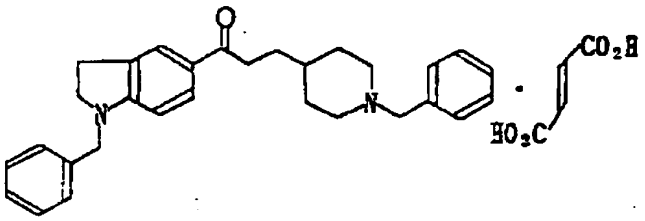
Elemental analysis, for $C_{17}H_{24}N_2O$			
Calcd.:	C, 74.96;	H, 8.88;	N, 10.29
Found :	C, 74.69;	H, 8.79;	N, 10.33

(4) Using 0.53 g of the compound obtained in (3), the procedure of Example 2 was followed to give 0.51 g of the free base of the title compound as a colorless oil. This oil (0.51 g) was treated with an equivalent of fumaric acid to give 0.57 g of the title fumarate as colorless crystals melting at 147 to 151 °C (decomp.).

Elemental analysis, for $C_{24}H_{30}N_2O \cdot C_4H_4O_4$			
Calcd.:	C, 70.27;	H, 7.18;	N, 5.85
Found :	C, 70.06;	H, 7.09;	N, 5.80

Example 15

2,3-Dihydro-5-[1-oxo-3-[1-(phenylmethyl)piperidin-4-yl]propyl]-1-(phenylmethyl)-1H-indole fumarate



(1) Using 0.65 g of the compound obtained in Example 14-(1), the procedure of Example 9-(2) was followed to give 0.77 g of 5-[3-(1-acetylpiperidin-4-yl)-1-oxopropyl]-2,3-dihydro-1-(phenylmethyl)-1H-indole as a colorless oil.

(2) Using 0.76 g of the compound obtained in (1), the procedure of Example 1 was followed to give 0.65 g of 2,3-dihydro-5-[1-oxo-3-(piperidin-4-yl)propyl]-1-(phenylmethyl)-1H-indole as a yellow oil.

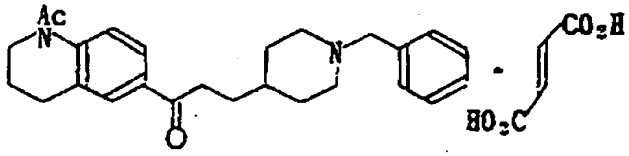
Elemental analysis, for $C_{23}H_{28}N_2O$			
Calcd.:	C, 79.27;	H, 8.10;	N, 8.04
Found :	C, 79.03;	H, 8.05;	N, 8.13

(3) Using 0.64 g of the compound obtained in (2), the procedure of Example 2 was followed to give 0.66 g of the free base of the title compound as a colorless oil. This oil (0.66 g) was treated with an equivalent of fumaric acid to give 0.75 g of the title fumarate as colorless crystals melting at 153 to 156°C (decomp.).

Elemental analysis, for $C_{30}H_{34}N_2O \cdot C_4H_4O_4$			
Calcd.:	C, 73.62;	H, 6.91;	N, 5.05
Found :	C, 73.65;	H, 6.80;	N, 5.00

Example 16

1-Acetyl-6-[1-oxo-3-[1-(phenylmethyl)piperidin-4-yl]propyl]-1,2,3,4-tetrahydroquinoline fumarate

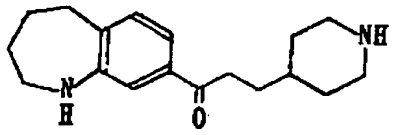


In 10 mℓ of dichloromethane were dissolved 0.5 g of 6-[1-oxo-3-[1-(phenylmethyl)piperidin-4-yl]propyl]-1,2,3,4-tetrahydroquinoline (free base), 0.28 g of acetic anhydride and 0.22 g of pyridine and the solution was refluxed for 2 hours. The solvent and the excess reagents were distilled off under reduced pressure and the residue was dissolved in dichloromethane. The solution was washed with 10% sodium hydroxide and dried over anhydrous sodium sulfate and the solvent was distilled off. This residue was purified by chromatography (eluent; ethyl acetate: ethanol = 20:1) to give 0.45 g of the free base of the title compound as a colorless oil. This oil, 0.45 g, was treated with an equivalent of fumaric acid to give 0.53 g of the title fumarate as an amorphous powder.

Elemental analysis, for $C_{26}H_{32}N_2O_2 \cdot C_4H_4O_4$			
Calcd.:	C, 69.21;	H, 6.97;	N, 5.38
Found :	C, 69.23;	H, 6.87;	N, 5.40

Example 17

8-[1-Oxo-3-(piperidin-4-yl)propyl]-2,3,4,5-tetrahydro-1H-1-benzazepine

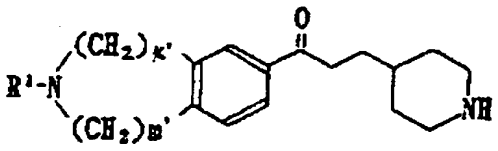


Using 6.5 g of the compound A obtained in Reference Exampel 4, the procedure of Example 1 was followed to give a viscous oil and this oil was crystallized from bexane to give 4.6 g of pale yellow crystals melting at 104 to 107 °C.

Elemental analysis, for $C_{18}H_{26}N_2O$			
Calcd.:	C, 75.48;	H, 9.15;	N, 9.78
Found :	C, 75.24;	H, 9.09;	N, 9.66

Example 18

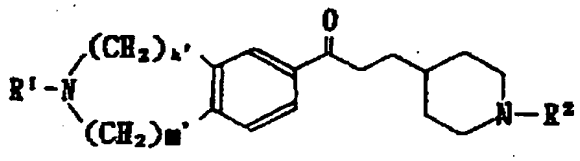
Using the compounds obtained in Reference Examples 4, 6 and 7, the procedure of Example 1 was followed to give compounds as oils as follows.

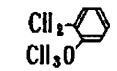
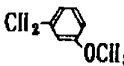
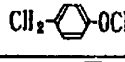
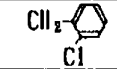
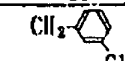
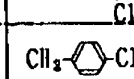
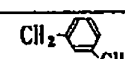
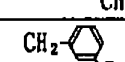
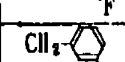


Compound No.	k'	m'	R^1	Molecular formula	Analysis Calcd. (Found)		
					C	H	N
1	2	0	C_2H_5	$C_{18}H_{26}N_2O$	75.48 (75.22	9.15 9.17	9.78 9.69)
2	2	0	C_3H_7	$C_{19}H_{28}N_2O$	75.96 (75.78	9.39 9.25	9.32 9.12)
3	2	0	C_4H_9	$C_{20}H_{30}N_2O$	76.39 (76.20	9.62 9.52	8.91 8.78)
4	2	0	C_5H_{11}	$C_{21}H_{32}N_2O$	76.78 (76.69	9.82 9.81	8.53 8.55)
5	2	0	CH_2CH_2Ph	$C_{24}H_{30}N_2O$	79.52 (79.46	8.34 8.11	7.73 7.59)
6	0	4	CH_3	$C_{19}H_{28}N_2O$	75.96 (75.84	9.39 9.29	9.32 9.33)
7	0	4	C_2H_5	$C_{20}H_{30}N_2O$	76.39 (76.21	9.62 9.51	8.91 8.75)
8	0	4	C_3H_7	$C_{21}H_{32}N_2O$	76.78 (76.53	9.82 9.74	8.53 8.41)
9	4	0	H	$C_{18}H_{26}N_2O$	75.48 (75.32	9.15 9.09	9.78 9.64)

Example 19

Using the compound obtained in Examples 12, 17 or 18, the procedure of Example 13 was followed to give the compounds as follows.



Compound No.	k'	m'	R^1	R^2	m.p. (°C)	Molecular formula	Analysis Calcd. (Found)		
							C	H	N
1	2	0	H		169-171 (decomp.)	$C_{24}H_{30}N_2O_2 \cdot C_4H_4O_4$*	68.00 (67.91	6.93 6.93	5.66 5.42)
2	2	0	H		151-153 (decomp.)	$C_{24}H_{30}N_2O_2 \cdot C_4H_4O_4$*	68.00 (67.71	6.93 6.77	5.66 5.56)
3	2	0	H		101-103	$C_{24}H_{30}N_2O_2 \cdot C_4H_4O_4$*	68.00 (67.79	6.93 6.92	5.66 5.61)
4	2	0	H		159-161	$C_{23}H_{27}ClN_2O \cdot C_4H_4O_4$*	64.99 (64.85	6.26 6.27	5.61 5.54)
5	2	0	H		157-159	$C_{23}H_{27}ClN_2O \cdot C_4H_4O_4$*	64.99 (64.91	6.26 6.31	5.61 5.57)
6	2	0	H		146-148	$C_{23}H_{27}ClN_2O \cdot C_4H_4O_4$*	64.99 (64.83	6.26 6.19	5.61 5.62)
7	2	0	H		169-163 (decomp.)	$C_{24}H_{30}N_2O \cdot C_4H_4O_4$*	70.27 (70.04	7.16 7.30	5.85 5.74)
8	2	0	H		163-165 (decomp.)	$C_{23}H_{27}FN_2O \cdot C_4H_4O_4$*	67.21 (67.03	6.48 6.50	5.81 5.76)
9	2	0	H		114-116	$C_{23}H_{27}N_3O_3$	70.21 (70.06	6.92 6.96	10.68 10.47)
10	2	0	H	CH_2CH_2Ph	143-145	$C_{24}H_{30}N_2O \cdot C_4H_4O_4$*	70.27 (69.98	7.16 7.22	5.85 5.74)
11	2	0	C_2H_5	CH_2Ph	155-157	$C_{25}H_{32}N_2O \cdot C_4H_4O_4$*	70.71 (70.55	7.37 7.43	5.69 5.54)
12	2	0	C_3H_7	CH_2Ph	91-93	$C_{26}H_{34}N_2O \cdot C_4H_4O_4$*	71.12 (71.00	7.56 7.62	5.53 5.33)

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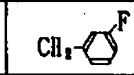
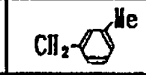
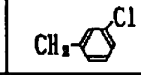
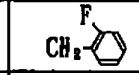
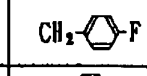
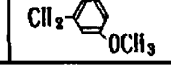
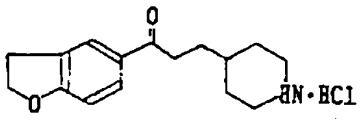
13	2	0	C_4H_9	CH_2Ph	127-129	$C_{27}H_{36}N_2O \cdot C_4H_4O_4$*	71.51 (71.29	7.74 7.86	5.38 5.22)
14	2	0	C_5H_{11}	CH_2Ph	140-142	$C_{28}H_{38}N_2O \cdot C_4H_4O_4$*	71.88 (71.71	7.92 8.13	5.24 5.12)
15	2	0	CH_2CH_2Ph	CH_2Ph	Amorphous solid	$C_{31}H_{38}N_2O \cdot C_4H_4O_4$*	73.92 (73.69	7.09 7.13	4.93 4.91)
16	0	4	H	CH_2Ph	173-174	$C_{25}H_{32}N_2O \cdot C_4H_4O_4$*	70.71 (70.54	7.37 7.47	5.69 5.57)
17	0	4	CH_3	CH_2Ph	100-102	$C_{26}H_{34}N_2O \cdot C_4H_4O_4$*	71.12 (70.97	7.56 7.55	5.53 5.48)
18	0	4	C_2H_5	CH_2Ph	84- 87	$C_{27}H_{36}N_2O \cdot C_4H_4O_4$*	71.51 (71.38	7.74 7.86	5.38 5.21)
19	0	4	C_3H_7	CH_2Ph	98-100	$C_{28}H_{38}N_2O \cdot C_4H_4O_4$*	71.88 (71.63	7.92 7.99	5.24 5.16)
20	4	0	H	CH_2Ph	117-120	$C_{25}H_{32}N_2O \cdot C_4H_4O_4$*	70.71 (70.59	7.37 7.48	5.69 5.43)
21	0	4	H		156-160	$C_{25}H_{31}N_2FO \cdot C_4H_4O_4$*	68.22 (67.88	6.91 6.95	5.49 5.27)
22	0	4	H		152-158	$C_{26}H_{34}N_2O \cdot C_4H_4O_4$*	71.12 (71.15	7.56 7.76	5.53 5.29)
23	0	4	H		138-144	$C_{25}H_{31}N_2ClO \cdot C_4H_4O_4$*	66.09 (66.00	6.69 6.92	5.32 4.98)
24	0	4	H		165-170	$C_{25}H_{31}N_2FO \cdot C_4H_4O_4$*	68.22 (68.04	6.91 6.92	5.49 5.24)
25	0	4	H		158-163	$C_{25}H_{31}N_2FO \cdot C_4H_4O_4$*	68.22 (67.99)	6.91 (6.82)	5.49 5.39)
26	0	4	H		126-128	$C_{26}H_{34}N_2O_2 \cdot C_4H_4O_4$*	68.94 (68.80	7.33 7.51	5.36 5.23)

27	0	4	H		116-117	$C_{26}H_{34}N_2O_2 \cdot C_4H_4O_4$*	68.94 (68.83	7.33 7.43	5.36 5.24
28	0	4	H		168-170	$C_{26}H_{34}N_2O_2 \cdot C_4H_4O_4$*	68.94 (68.78	7.33 7.44	5.36 4.84)
29	0	4	H		161-163	$C_{25}H_{31}N_3O_3 \cdot C_4H_4O_4$*	64.79 (64.81	6.56 6.40	7.82 7.66)
30	2	0	H		144-147	$C_{23}H_{27}FN_2O \cdot C_4H_4O_4$*	67.21 (67.13	6.48 6.44	5.81 5.73)
31	2	0	H		124-127	$C_{23}H_{27}FN_2O \cdot C_4H_4O_4$*	67.21 (67.09	6.48 6.51	5.81 5.69)
32	0	4	CH_2Ph	CH_2Ph	171-173	$C_{32}H_{38}N_2O \cdot C_4H_4O_4$*	74.20 (74.08	7.26 7.33	4.81 4.85)

* : $C_4H_4O_4$ means the fumarate.
Ph means phenyl.
Me means methyl.
Ac means acetyl.

Example 20

2,3-Dihydro-5-[1-oxo-3-(piperidin-4-yl)propylbenzofuran hydrochloride

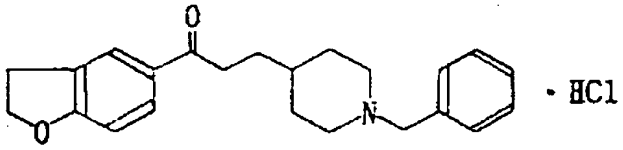


To 30 ml of concentrated hydrochloric acid was added 5.00 g of 5-[3-(1-acetylpiperidin-4-yl)-1-oxopropyl]-2,3-dihydrobenzofuran, and the mixture was refluxed for 14 hours. The reaction mixture was left standing for cooling and then made basic with a dilute aqueous solution of sodium hydroxide, followed by extraction with methylene chloride. Organic layers were combined and dried over anhydrous sodium sulfate, then the solvent was distilled off to leave 4.31 g (100%) of 2,3-dihydro-5-[1-oxo-3-(piperidin-4-yl)propyl]-benzofuran (4). The solid matter thus obtained was dissolved in methanol, treated with hydrogen chloride and recrystallized from methanol - ethyl acetate to gave colorless needles, m.p. 203-205 °C (decomp.)

Elemental Analysis, for $C_{16}H_{21}NO_2 \cdot HCl$			
Calcd.:	C, 64.97;	H, 7.50;	N, 4.74
Found :	C, 64.76;	H, 7.64;	N, 4.54

Example 21

2,3-Dihydro-5-[1-oxo-3-[1-(phenylmethyl)piperidin-4-yl]propyl]benzofuran hydrochloride

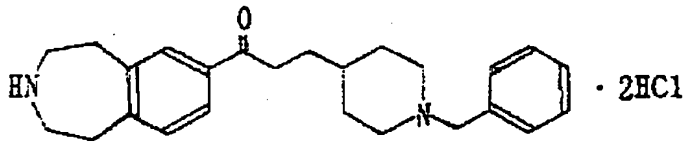


To 30 ml of a mixture solution of tetrahydrofuran and ethanol (50/50 = v/v) was added 1.52 g of 2,3-dihydro-5-[1-oxo-3-(piperidin-4-yl)propyl]benzofuran, to which was then added 1.08 g of potassium carbonate. The resultant mixture was ice-cooled and there was added dropwise an ethanol solution (5 ml) of 0.96g of benzyl bromide. The mixture was stirred for 22 hours at room temperatures, then the solvent was distilled off. To the residue was added water, which was extracted with methylene chloride. Organic layers were combined and dried over anhydrous sodium sulfate, then the solvent was distilled off. The residue was purified by means of a silica gel column chromatography (ethyl acetate) to give 1.13 g (55%) of 2,3-dihydro-5-[1-oxo-3-[1-(phenylmethyl)piperidin-4-yl]propylbenzofuran. The product was dissolved in methanol, treated with hydrogen chloride, then recrystallized from ethanol - ethyl acetate to give colorless needles (1/4 hydrate), m.p. 143-144 °C.

Elemental Analysis for $C_{23}H_{27}NO_2 \cdot HCl.1/4H_2O$:			
Calcd.:	C, 70.75;	H, 7.36;	N, 3.59
Found :	C, 70.49;	H, 7.26;	N, 3.62

Example 22

7-[1-Oxo-3-[1-(phenylmethyl)piperidin-4-yl]propyl]-2,3,4,5-tetrahydro-1H-3-benzazepine dihydrochloride

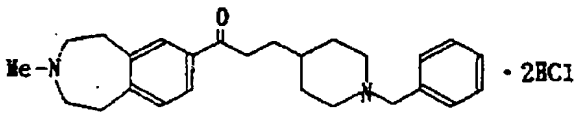


Under nitrogen atomosphere, 0.48 g (1.1 mmol.) of 3-methoxycarbonyl-7-[3-(1-benzoylpiperidin-4-yl)-1-yl)oxopropyl]-2,3,4,5-tetrahydro-1H-3-benzazepine obtained in Reference Example 11 was dissolved in 5 ml of dry chloroform. To the solution was added 0.3 ml (2.1 mmol.) of iodotrimethylsilane. The mixture was stirred for 2.5 hours at 50°C. The reaction mixture was left standing for cooling, to which was added 0.4 ml (10 mmol.) of methanol. To the resultant mixture were added a dilute aqueous solution of sodium hydroxide and an aqueous solution of sodium thiosulfate, followed by extraction with dichloromethane. The extract was dried over anhydrous sodium sulfate, then the solvent was distilled off. The residue was dissolved in 15 ml of dry tetrahydrofuran. To the solution was added 0.13 g (3.4 mmol.) of lithium aluminum hydride, and the mixture was refluxed for 5 hours. To the reaction mixture was added water, then the solid matter was filtered off. The filtrate was dried over anhydrous sodium sulfate, then the solvent was distilled off. The residue was dissolved in methanol and treated with hydrogen chloride and the solvent was distilled off to give a hydrochloride. To the hydrochloride there was further added a mixture of 0.3 g (3 mmol.) of chromic acid, 0.3 ml of concentrated sulfuric acid and 10 ml of water-acetone (1/1 = v/v). The resultant mixture was stirred for 24 hours at room temperatures. The reaction mixture was poured into water and it was made basic with a dilute aqueous solution of sodium hydroxide, followed by extraction with dichloromethane. The extract was dried over anhydrous sodium sulfate, then the solvent was distilled off. The residue was purified by means of an alumina column chromatography to give 0.31 g (76%) of 7-[1-oxo-3-[1-(phenylmethyl)-piperidin-4-yl]propyl]-2,3,4,5-tetrahydro-1H-3-benzazepine. The product was dissolved in methanol and treated with 3 N methanolic hydrochloric acid to give dihydrochloride as an amorphous powder.

Elemental Analysis, for $C_{25}H_{32}N_2O \cdot 2HCl \cdot 2.5H_2O$:			
Calcd.:	C, 60.72;	H, 7.95;	N, 5.66
Found :	C, 60.85;	H, 8.24;	N, 5.51

Example 23

3-Methyl-7-[1-oxo-3-[1-(phenylmethyl)piperidin-4-yl]-propyl]-2,3,4,5-tetrahydro-1H-3-benzazepine dihydrochloride



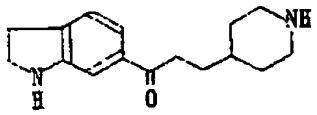
In 40 ml of toluene was dissolved 1.17 g (2.6 mmol.) of 3-methoxycarbonyl-7-[3-(1-benzoylpiperidin-4-yl)-1-oxopropyl]-2,3,4,5-tetrahydro-1H-3-benzazepine. To the solution were added 7 ml of ethylene glycol and 10 mg of p-toluenesulfonic acid, and the mixture was refluxed for 2.5 hours. To the reaction mixture was added a saturated aqueous solution of sodium hydrogen carbonate, which was subjected to extraction with diethyl ether. The extract was dried over anhydrous sodium sulfate, then the solvent was distilled off. The residue was purified by means of a silica gel column chromatography to give 1.22 g (94%) of 7-[2-[2-(1-benzoylpiperidin-4-yl)ethyl]-1,3-dioxoran-2-yl]-3-methoxycarbonyl-2,3,4,5-tetrahydro-1H-3-benzazepine.
1.03 g (2.1 mmol.) of the compound obtained above was dissolved in 15 ml of dry tetrahydrofuran, to which was added 0.25 g (6.5 mmol.) of lithium aluminum hydride. The reaction mixture was refluxed for 3 hours and there was added water, followed by filtration. The filtrate was dried over anhydrous sodium sulfate, then the solvent was distilled off. The residue was dissolved in tetrahydrofuran, to which was added 5.6 ml of 1N-HCl, and the mixture was stirred for 14.5 hours at room temperature. The reaction mixture was made basic

with a dilute aqueous solution of sodium hydroxide, followed by extraction with dichloromethane. The extract solution was dried over anhydrous sodium sulfate, then the solvent was distilled off. The residue was dissolved in methanol and the solution was treated with hydrogen chloride to give a dihydrochloride, which was then recrystallized from ethanol - ethyl acetate to give 0.65 g (67%) of colorless needles, m.p. 190-193°C.

Elemental Analysis for $C_{25}H_{34}N_2O \cdot 2HCl \cdot H_2O$:			
Calcd.:	C, 64.86;	H, 7.95;	N, 5.82
Found :	C, 64.78;	H, 7.90;	N, 5.78

Example 24

2,3-Dihydro-6-[1-oxo-3-(piperidin-4-yl)propyl]-1H-indole

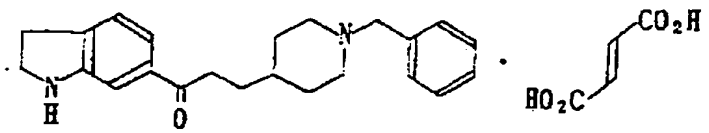


(1) To a mixture of 25 g of 2,3-dihydro-1-trifluoroacetyl-indole, 25 g of 3-(1-acetylpiperidin-4-indole)-propionic acid chloride and 120 ml of carbon disulfide was added 58 g of anhydrous aluminum chloride at room temperatures, then the mixture was refluxed for 30 hours. The reaction mixture was treated in a manner like that of Reference Example 1-(3) to give 9.0 g of a mixture of 6-[3-(1-acetylpiperidin-4-yl)-1-oxopropyl]-2,3-dihydro-1-trifluoroacetyl-1H-indole and 5-[3-(1-acetylpiperidin-4-yl)-1-oxopropyl]-2,3-dihydro-1-trifluoroacetyl-1H-indole as a pale yellow oily product.
(2) The oily product obtained in (1) was subjected to a reaction like that of Example 1 to give 2,3-dihydro-6-1-oxo-3-(piperidin-4-yl)propyl]-1H-indole dihydrochloride. A mixture of this dihydrochloride and 2,3-dihydro-5-1-oxo-3-(piperidin-4-yl)propyl]-1H-indole dihydrochloride was subjected to recrystallization twice from methanol - ethyl acetate to give 2.5 g of dihydrochloride of the above-titled compound as colorless powder, m.p. 146-148°C. The powdery compound thus obtained was dissolved in water, whose pH was adjusted to about 10 with a 10% sodium hydroxide solution, which was subjected to extraction with dichloromethane. The extract solution was dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure to give 1.8 g of the above-titled compound as a pale yellow oily product.

Elemental Analysis, for $C_{16}H_{22}N_2O$:			
Calcd.:	C, 74.38;	H, 8.58;	N, 10.84
Found :	C, 74.32;	H, 8.66;	N, 10.74

Example 25

2,3-Dihydro-6-[1-oxo-3-[1-(phenylmethyl)piperidin-4-yl]propyl]-1H-indole fumarate

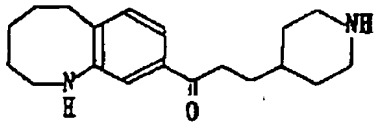


Using 0.5 g of the compound obtained in Example 24, the procedure of Example 13 was followed to give 0.55 g of the title compound as colorless crystals, m.p. 157-158 °C.

Elemental Analysis for $C_{23}H_{28}N_2O.C_4H_4O_4$:			
Calcd.:	C, 69.81;	H, 6.94;	N, 6.03
Found :	C, 69.65;	H, 6.87;	N, 5.76

Example 26

9-[1-Oxo-3-(piperidin-4-yl)propyl]-1,2,3,4,5,6-hexahydro-1-benzazocine

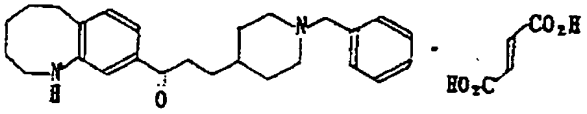


Using 1-ethoxycarbonyl-1,2,3,4,5,6-hexahydro-1-benzazocine, the procedure of Reference Example 2-(2) was followed to give a residue. The residue was subjected to similar reaction to Example 1 to give the title compound as a pale yellow oily product.

Elemental Analysis, for $C_{19}H_{28}N_2O$:			
Calcd.:	C, 75.95;	H, 9.39;	N, 9.33
Found :	C, 75.73;	H, 9.38;	N, 9.10

Example 27

9-[1-Oxo-3-[1-(phenylmethyl)piperidin-4-yl]propyl]-1,2,3,4,5,6-hexahydro-1-benzazocine fumarate

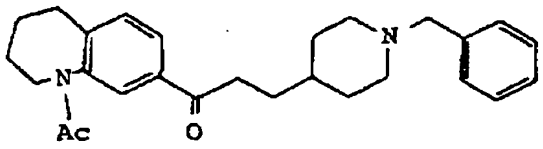


Using 9-[1-oxo-3-(piperidin-4-yl)propyl]-1,2,3,4,5,6-hexahydro-1-benzazocine, the procedure of Example 13 was followed to give the title compound as colorless crystals.

Elemental Analysis, for $C_{26}H_{34}N_2O \cdot C_4H_4O_4$:			
Calcd.:	C, 71.12;	H, 7.56;	N, 5.53
Found :	C, 70.98;	H, 7.61;	N, 5.42

Example 28

1-Acetyl-8-[1-oxo-3-[1-(phenylmethyl)piperidin-4-yl]propyl]-2,3,4,5-tetrahydro-1H-1-benzazepine

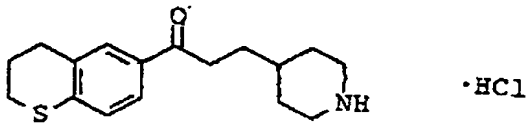


Using 0.3 g of 8-[1-oxo-3-[1-(phenylmethyl)piperidin-4-yl]propyl]-2,3,4,5-tetrahydro-1H-1-benzazepine, which is a free base of the compound obtained in Example 19 compound No. 16, the procedure of Example 16 was followed to give 0.21 g of the title compound as a colorless powder, m.p. 115-116°C.

Elemental Analysis, for $C_{27}H_{34}N_2O_2$			
Calcd.:	C, 77.48;	H, 8.19;	N, 6.69
Found :	C, 77.21;	H, 7.98;	N, 6.56

Example 29

3,4-Dihydro-6-[1-oxo-3-(piperidin-4-yl)propyl]-2H-1-benzothiopyran hydrochloride

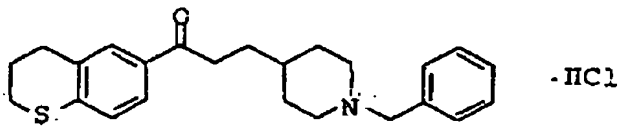


Using 2.5 g of the compound obtained in Reference Example 12, the procedure of Example 1 was followed to give 2.4g of the title compound as a colorless powder, m.p. 196-199°C.

Elemental analysis, for $C_{24}H_{29}NOS \cdot HCl$:			
Calcd.:	C, 62.65;	H, 7.42;	N, 4.30
Found :	C, 62.61;	H, 7.33;	N. 4.27

Example 30

3,4-Dihydro-6-[1-oxo-3-[1-(phenylmethyl)piperidin-4-yl]propyl]-2H-1-benzothiopyran hydrochloride

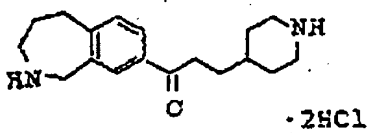


Using 0.83g of the compound obtained in Example 29, the procedure of Example 2 was followed to give 1.0g of the title compound as a colorless powder, m.p. 186-188°C.

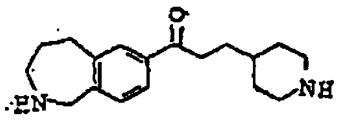
Elemental analysis, for $C_{24}H_{29}NOS \cdot HCl$:			
Calcd.:	C, 69.29;	H, 7.27;	N, 3.37
Found :	C, 69.31;	H, 7.22;	N, 3.27

Example 31

8-[1-Oxo-3-(piperidin-4-yl)propyl]-2,3,4,5-tetrahydro-1H-2-benzazepine dihydrochloride (A) and 7-[1-oxo-3-(piperidine-4-yl)propyl]-2,3,4,5-tetrahydro-1H-2-benzazepine dihydrochloride (B)



(A)



(B)

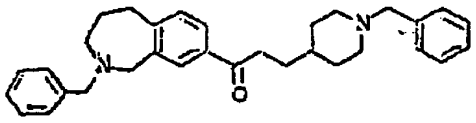
Using 5.0 g of 2-acetyl-2,3,4,5-tetrahydro-1H-2-benzazepine, the procedure of Reference Example 1 was followed to give 4.7 9 of a viscous oil.

Using 4.5 g of the oil, the procedure of Example 1 was followed to give 3.3 g of a pale yellow solid. The solid was recrystallized from methanol to give the title compound (A) as colorless powder, m.p.>300 °C.

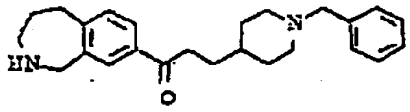
Elemental analysis, for $C_{18}H_{26}N_2O \cdot 2HCl$:			
Calcd.:	C, 60.17;	H, 7.85;	N, 7.80.
Found :	C, 59.05;	H, 7.98;	N, 7.77.

Example 32

8-[1-Oxo-3-[1-(phenylmethyl)piperidin-4-yl]propyl]-2-(phenylmethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine dihydrochloride (A) and 8-[1-oxo-3-[1-(phenylmethyl)piperidin-4-yl]propyl]-2,3,4,5-tetrahydro-1H-2-benzazepine dihydrochloride (B)



(A)



(B)

Using 1.5 g of 8-[1-oxo-3-(piperidin-4-yl)propyl]-2,3,4,5-tetrahydro-1H-2-benzazepine Dihydrochloride obtained in Example 31, the procedure of Example 2 was followed to give 0.5 g of the title compound (A) as an amorphous powder and 0.1 g of the title compound (B) as an amorphous powder.

8-[1-Oxo-3-(1-(phenylmethyl)piperidin-4-yl)propyl]-2-(phenylmethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine dihydrochloride (A)

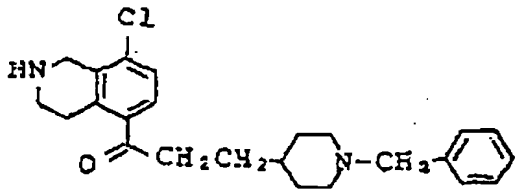
Elemental analysis, for $C_{32}H_{38}N_2O \cdot 2HCl$:			
Calcd.:	C, 71.23;	H, 7.47;	N, 5.19.
Found :	C, 66.72;	H, 7.69;	N, 6.01.

8-[1-Oxo-3-(1-(phenylmethyl)piperidin-4-yl)propyl]-2,3,4,5-tetrahydro-1H-2-benzazepine dihydrochloride (B)

Elemental analysis, for $C_{25}H_{32}N_2O \cdot 2HCl$:			
Calcd.:	C, 66.81;	H, 7.62;	N, 6.23.
Found :	C, 66.72;	H, 7.69;	N, 6.01.

Example 33

8-Chloro-5-[1-oxo-3-[1-(phenylmethyl)piperidin-4-yl)propyl]-1,2,3,4-tetrahydroisoquinoline Dihydrochloride



To a solution of 5.99 g (13.22 mmol) of the compound obtained in Reference Example 14 in 198 ml of methanol was added 99 ml of 1N aqueous NaOH. THe mixture was stirred at 60°C far 5 hours. After removal of methanol under reduced pressure, the aqueos residue was extracted with dichloromethane. The extracts were dried over anhydrous sodium sulfate and the solvent was distilled off. The residue was purified by means of a silica gel column chromatography (eluent; ethyl acetate:methanol = 7:3(v/v)) to give 2.59 g of 5-[3-(1-benzoylpiperidin-4-yl)-1-oxopropyl]-8-chloro-1,2,3,4-tetrahydroisoquinoline.

To a solution of 1.23 g (3.0 mmol) of the compound obtained above in 10 ml of methanol was added 0.75 ml of 4N methanolic HCl at 5°C and the solvent was distilled off. To the residual oil was added 60 ml of toluene, 8.24 ml of ethylene glycol, and 57 mg of p-toluenesulfonic acid monohydrate. The mixture was refluxed for 2 hours. To the, reaction mixture was added a saturated aqueous solution of $NaHCO_3$, which was subjected to extraction with dichloromethane. The extracts were dried over anhydrous sodium sulfate, then the solvent removed under reduced pressure. The residue was purified by means of a silica gel column chromatography (eluent; ethyl acetate: methanol = 7:3(v/v) to give 1.31 g of 5-[2-[2-(1-benzoylpiperidin-4-yl)ethyl]-1,3-dioxoran-2-yl]-8-chloro-1,2,3,4-tetrahydroisoquinoline.

Under nitrogen atmosphere, to a solution of 455 mg (1.0 mg) of the compound obtained above in 10 ml of dry tetrahydrofuran was added 127μl of chloro trimethylsilane at 5°C and the mixture was stirred at room temperature for 1 hour. Then to the reaction mixture was added 190 mg of lithium aluminum hydride and the mixture was refluxed for 2.5 hours. Water was added to mixture and the resulting precipitate was removed by filtration. The filtrate was dried over anhydrous sodium sulfate, and the solvent was removed under seduced pressure. A mixture of the residue and 5 ml of 1N aqueous HCl in 5 ml of tetrahydrofuran was heated at 60°C for 3 hours. The reaction mixture was made basic with a dilute aqueous NaOH, followed by extraction with dichloromethane. The extract was dried over anhydrous sodium sulfate, then the solvent was removed under reduced pressure to give 200 mg of a colorless oil, which was treated with 4N-methanolic HCl (2 equivalent) to give 205 mg of the title compound as an amorphous powder.

Elemental analysis, for $C_{24}H_{29}ClN_2O \cdot 2HCl$:			
Calcd.:	C,61.35;	H,6.65;	N,5.98.
Found :	C,61.42;	H,6.69;	N,5.91.

Formulation Example 1

(1) 8-[3-[1-(Phenylmethyl)piperidin-4-yl]-1-oxopropyl]-1,2,3,4-tetrahydroquinoline bihydrochloride (the compound obtained in Example 2)	1 g
(2) Lactose	197 g
(3) Corn starch	50 g
(4) Magnesium stearate	2 g

(1), (2) and 20 g of corn starch were blended and the mixture was granulated with a paste prepared from 15 g of corn starch and 25 ml of water. To this granular product were added 15 g of corn starch and (4) and the resulting composition was compression-molded to provide 2000 tables each measuring 3 mm in diameter and containing 0.5 mg of (1).

Formulation Example 2

(1) 8-[3-[1-(Phenylmethyl)piperidin-4-yl]-1-oxopropyl]-1,2,3,4-tetrahydroquinoline dihydrochloride (the compound obtained in Example 2)	2 g
(2) Lactose	196 g
(3) Corn starch	50 g
(4) Magnesium stearate	2 g

(1), (2) and 20 g of corn starch were blended and the mixture was granulated with a paste prepared from 15 g of corn starch and 25 ml of water. To this granular product were added 15 g of corn starch and (4) and the resulting composition was compression-molded to provide 2000 tablets each measuring 5 mm in diameter and containing 1 mg of (1).

Formulation Example 3

(1) 8-[1-Oxo-3-[1-(Phenylmethyl)piperidin-4-yl]propyl]-2,3,4,5-tetrahydro-1H-1-benzazepine fumarate (the compound obtained in Example 19 compound No. 16)	1 g
(2) Lactose	197 g
(3) Corn starch	50 g
(4) Magnesium stearate	2 g

(1), (2) and 20 g of corn starch were blended and the mixture was granulated with a paste prepared from 15 g of corn starch and 25 ml of water. To this granular product were added 15 g of corn starch and (4) and the resulting composition was compression-molded to provide 1000 tablets each measuring 3 mm in diameter and containing 1.0 mg of (1).

Formulation Example 4

(1) 7-[1-Oxo-3-[1-(phenylmethyl)piperidin-4-yl]propyl]-2,3,4,5-tetrahydro-1H-3-benzazepine dihydrochloride (the compound obtained in Example 22)	2 g
(2) Lactose	196 g
(3) Corn starch	50 g
(4) Magnesium stearate	2 g

(1), (2) and 20 g of corn starch were blended and the mixture was granulated with a paste prepared from 15 g of corn starch and 25 ml of water. To this granular product were added 15 g of corn starch and (4) and the resulting composition was compression-molded to provide 2000 tablets each measuring 5 mm in diameter and containing 1 mg of (1).

Formulation Example 5

8-[1-Oxo-3-[1-(phenylmethyl)piperidin-4-yl]propyl]-2,3,4,5-tetrahydro-1H-1-benzazepine fumarate (the compound obtained in Example 19, compound No. 16) (2 g) and 1.25g of mannitol were dissolved in 500 mℓ of distilled water, pH was adjusted to 5.6 to 7 with 0.1N NaOH and the total amount of the solution was made up to 1000 mℓ. The solution thus obtained was sterilized by filtration through a filter of 0.2μm. The resulting solution was distributed to provide 1000 of 1mℓ-ampoules.

Experimental Example

The cholinesterase inhibitory activity of the compound of the present invention was assayed with (acetyl-[3H])-acetylcholine. Thus, using the S_1 fraction of a homogenate of male Wistar rat cerebral cortex as the cholinesterase source, (acetyl-[3H])-acetylcholine and the compound of the invention were added as the substrate and the test substance, respectively, and the mixture was incubated for 30 minutes. After the reaction was terminated, a toluene-based scintillant was added and, after shaking, the reaction product [3H]-acetic acid which was transferred to the toluene layer was determined with a scintillation counter to estimate the cholinesterase activity.
The cholinesterase inhibitory activity of the test compound was expressed in 50% inhibitory concentration (IC_{50}). The cholinesterase inhibitory activity of physostigmine was also determined by the same procedure. The results are shown in Table 1.

[Table 1]

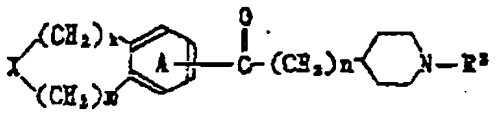
Compound (Example No.)	Acetylcholinesterase inhibitory activity IC_{50} (μM)
2	0.014
3	0.12
4	0.010
6-A	0.054
6-B	0.054
8-A	0.024
8-B	0.036
10	0.16
13	0.020
14	0.010
15	0.068
16	0.014
19-4	0.076
19-5	0.059
19-7	0.050
19-8	0.016
19-9	0.064
19-11	0.011
19-12	0.022
19-13	0.029
19-14	0.047
19-15	0.028
19-16	0.102
19-17	0.081
19-20	0.125
19-21	0.145
21	0.028
22	0.0076
23	0.0065
25	0.113
27	0.127
Physostigmine	0.22

The above results indicate that the compound of the present invention has excellent cholinesterase inhibitory activity.

The compound of the present invention has effects on the central nervous system of mammalian animals and exhibits potent cholinesterase inhibitory activity. Therefore, the compound can be used for the prevention and treatment of senile dementia, Alzheimer's disease, Huntington's chorea and other diseases related to brain dysfunction and is, therefore, of value as a medicament.

Claims

1. A condensed heterocyclic compound of the formula (I):



(I)

wherein X is an oxygen atom, a sulfur atom or R^1-N< wherein R^1 is a hydrogen atom, a hydrocarbon group which may be substituted or an acyl group which may be substituted; R^2 is a hydrogen atom or a hydrocarbon group which may be substituted; ring A is a benzene ring which may be substituted; k is a whole number of 0 to 3; m is a whole number of 1 to 8; and n is a whole number of 1 to 6, or a salt thereof.

2. A compound as claimed in claim 1, wherein X is R^1-N< wherein R^1 is as defined in claim 1.

3. A compound as claimed in claim 2, wherein k is 0 and m is 2 to 7.

4. A compound as claimed in claim 1, wherein R^1 is a hydrogen atom.

5. A compound as claimed in claim 1, wherein R^1 is a hydrocarbon group which may be substituted.

6. A compound as claimed in claim 1, wherein R^1 is an acyl group which may be substituted.

7. A compound as claimed in claim 1, wherein R^2 is a hydrocarbon group which may be substituted.

8. A compound as claimed in claim 1, wherein the hydrocarbon group denoted by R^1 and R^2 is ① a straight-chain or branched C_{1-11} alkyl, C_{2-4} alkenyl or C_{2-4} alkynyl group, ② a C_{3-7} monocyclic cycloalkyl group, ③ a C_{8-14} bridged cyclic saturated hydrocarbon group, ④ a phenyl or naphthyl group or ⑤ a C_{7-18} aralkyl, C_{8-18} arylalkenyl, C_{8-18} arylalkynyl or C_{3-7} cycloalkyl-C_{1-6} alkyl group and the acyl group denoted by R^1 is ① a C_{2-6} alkylcarbonyl or phenylcarbonyl, ② a C_{1-7} alkylsulfonyl or phenylsulfonyl, ③ a C_{1-7} alkylphosphonyl or phenylphosphonyl or ④ a C_{2-8} alkyloxycarbonyl or C_{7-8} aralkyloxy-carbonyl group.

9. A compound as claimed in claim 1, wherein R^1 is ① a hydrogen atom, ② a straight-chain or branched C_{1-11} alkyl, C_{2-4} alkenyl or C_{2-4} alkynyl group which may be substituted by 1 to 5 substituents selected from the group consisting of a halogen, nitro, cyano, hydroxy, C_{1-4} alkoxy, C_{1-4} alkylthio, amino, mono- or di-C_{1-4} alkyl-substituted amino, cyclic amino, C_{1-4} alkylcarbonylamino, C_{1-4} alkylsulfonylamino, C_{1-4} alkoxycarbonyl, C_{1-6} alkylcarbonyl, carbamoyl, mono- or di-C_{1-4} alkyl-substituted carbamoyl and C_{1-6} alkylsulfonyl, ③ a C_{3-7} monocyclic cycloalkyl group which may be substituted by 1 to 5 substituents selected from the group consisting of a halogen, nitro, cyano, hydroxy, C_{1-4} alkoxy, C_{1-4} alkylthio, amino, mono-or di-C_{1-4} alkyl-substituted amino, cyclic amino, C_{1-4} alkylcarbonylamino, C_{1-4} alkylsulfonylamino, C_{1-4} alkoxycarbonyl, C_{1-6} alkylcarbonyl, carbamoyl, mono- or di-C_{1-4} alkyl-substituted carbamoyl and C_{1-6} alkylsulfonyl, ④ a C_{8-14} bridged cyclic saturated hydrocarbon group which may be substituted by 1 to 5 substituents selected from the group consisting of a halogen, nitro, cyano, hydroxy, C_{1-4} alkoxy, C_{1-4} alkylthio, amino, mono- or di-C_{1-4} alkyl-substituted amino, cyclic amino, C_{1-4} alkylcarbonylamino, C_{1-4} alkylsulfonylamino, C_{1-4} alkoxycarbonyl, C_{1-6} alkylcarbonyl, carbamoyl, mono- or di-C_{1-4} alkyl-substituted carbamoyl and C_{1-6} alkylsulfonyl, ⑤ a phenyl or naphthyl group which may be substituted by 1 to 3 substituents selected from the group consisting of a C_{1-4} alkyl, halogen, nitro, cyano, hydroxy, C_{1-4} alkoxy, C_{1-4} alkylthio, amino, mono- or di-C_{1-4} alkyl-substituted amino, cyclic amino, C_{1-4} alkylcarbonylamino, aminocarbonyloxy, mono- or di-C_{1-4} alkyl-substituted aminocarbonyloxy, C_{1-4} alkylsulfonylamino, C_{1-4} alkoxycarbonyl, hydroxycarbonyl, C_{1-6} alkylcarbonyl, C_{3-6} cycloalkylcarbonyl, carbamoyl, mono- or di-C_{1-4} alkyl-substituted carbamoyl, C_{1-6} alkylsulfonyl, C_{3-6} cycloalkylsulfonyl and a phenyl, naphthyl, phenoxy, benzoyl, phenoxycarbonyl, phenyl-C_{1-4} alkylcarbamoyl, phenylcarbamoyl, phenyl-C_{1-4} alkylcarbonylamino, benzoylamino, phenyl-C_{1-4} alkylsulfonyl, phenylsulfonyl, phenyl-C_{1-4} alkylsulfinyl, phenyl-C_{1-4} alkylsulfonylamino or phenylsulfonylamino which may be substituted by 1 to 4 substituents selected from the group consisting of a C_{1-4} alkyl, C_{1-4} alkoxy, halogen, hydroxy, benzyloxy, amino, mono- or di-C_{1-4} alkyl-substituted amino, nitro and C_{1-4} alkylcarbonyl, ⑥ a C_{7-18} aralkyl, C_{8-18} arylalkenyl, C_{8-18} arylalkynyl or C_{3-7} cycloalkyl-C_{1-6} alkyl group which may be substituted by 1 to 5 substituents selected from the group

consisting of a C_{1-4} alkyl, halogen, nitro, cyano, hydroxy, C_{1-4} alkoxy, C_{1-4} alkylthio, amino, mono- or di-C_{1-4} alkyl-substituted amino, cyclic amino, C_{1-4} alkylcarbonylamino, aminocarbonyloxy, mono- or di-C_{1-4} alkyl-substituted aminocarbonyloxy, C_{1-4} alkylsulfonylamino, C_{1-4} alkoxycarbonyl, hydroxycarbonyl, C_{1-6} alkylcarbonyl, C_{3-6} cycloalkylcarbonyl, carbamoyl, mono- or di-C_{1-4} alkyl-substituted carbamoyl, C_{1-6} alkylsulfonyl, C_{3-6} cycloalkylsulfonyl and a phenyl, naphthyl, phenoxy, benzoyl, phenoxycarbonyl, phenyl-C_{1-4} alkylcarbamoyl, phenylcarbamoyl, phenyl-C_{1-4} alkylcarbonylamino, benzoylamino, phenyl-C_{1-4} alkylsulfonyl, phenylsulfonyl, phenyl-C_{1-4} alkylsulfinyl, phenyl-C_{1-4} alkylsulfonylamino or phenylsulfonylamino which may be substituted by 1 to 4 substituents selected from the group consisting of a C_{1-4} alkyl, C_{1-4} alkoxy, halogen, hydroxy, benzyloxy, amino, mono- or di-C_{1-4} alkyl-substituted amino, nitro and C_{1-6} alkylcarbonyl, ⑦ a C_{2-8} alkylcarbonyl or phenylcarbonyl group which may be substituted by 1 to 3 substituents selected from the group consisting of a halogen, amino, C_{1-6} alkyl- or C_{3-6} cycloalkyl-substituted primary or secondary amino and C_{1-4} alkoxy, ⑧ a C_{1-7} alkylsulfonyl or phenylsulfonyl group which may be substituted by 1 to 3 substituents selected from the group consisting of a halogen, amino, C_{1-6} alkyl- or C_{3-6} cycloalkyl-substituted primary or secondary amino and C_{1-4} alkoxy, ⑨ a C_{1-7} alkylphosphonyl or phenylphosphonyl group which may be substituted by 1 to 3 substituents selected from the group consisting of a halogen, amino, C_{1-6} alkyl- or C_{3-6} cycloalkyl-substituted primary or secondary amino and C_{1-4} alkoxy, or ⑩ a C_{2-8} alkyloxycarbonyl or C_{7-8} aralkyloxy-carbonyl group which may be substituted by 1 to 3 substituents selected from the group consisting of a halogen, amino, C_{1-6} alkyl- or C_{2-6} cycloalkyl-substituted primary or secondary amino and C_{1-4} alkoxy; R^2 is ① a hydrogen atom, ② a straight-chain or branched C_{1-11} alkyl, C_{2-4} alkenyl or C_{2-4} alkynyl group which may be substituted by 1 to 5 substituents selected from the group consisting of a halogen, nitro, cyano, hydroxy, C_{1-4} alkoxy, C_{1-4} alkylthio, amino, mono-or di-C_{1-4} alkyl-substituted amino, cyclic amino, C_{1-4} alkylcarbonylamino, C_{1-4} alkylsulfonylamino, C_{1-4} alkoxycarbonyl, C_{1-6} alkylcarbonyl, carbamoyl, mono- or di-C_{1-4} alkyl-substituted carbamoyl and C_{1-6} alkylsulfonyl, ③ a C_{3-7} monocyclic cycloalkyl group which may be substituted by 1 to 5 substituents selected from the group consisting of a halogen, nitro, cyano, hydroxy, C_{1-4} alkoxy, C_{1-4} alkylthio, amino, mono-or di-C_{1-4} alkyl-substituted amino, cyclic amino, C_{1-4} alkylcarbonylamino, C_{1-4} alkylsulfonylamino, C_{1-4} alkoxycarbonyl, C_{1-6} alkylcarbonyl, carbamoyl, mono- or di-C_{1-4} alkyl-substituted carbamoyl and C_{1-6} alkylsulfonyl, ④ a C_{8-14} bridged cyclic saturated hydrocarbon group which may be substituted by 1 to 5 substituents selected from the group consisting of a halogen, nitro, cyano, hydroxy, C_{1-4} alkoxy, C_{1-4} alkylthio, amino, mono- or di-C_{1-4} alkyl-substituted amino, cyclic amino, C_{1-4} alkylcarbonylamino, C_{1-4} alkylsulfonylamino, C_{1-4} alkoxycarbonyl, C_{1-6} alkylcarbonyl, carbamoyl, mono- or di-C_{1-4} alkyl-substituted carbamoyl and C_{1-6} alkylsulfonyl, ⑤ a phenyl or naphthyl group which may be substituted by 1 to 3 substituents selected from the group consisting of a C_{1-4} alkyl, halogen, nitro, cyano, hydroxy, C_{1-4} alkoxy, C_{1-4} alkylthio, amino, mono- or di-C_{1-4} alkyl-substituted amino, cyclic amino, C_{1-4} alkylcarbonylamino, aminocarbonyloxy, mono- or di-C_{1-4} alkyl-substituted aminocarbonyloxy, C_{1-4} alkylsulfonylamino, C_{1-4} alkoxycarbonyl, hydroxycarbonyl, C_{1-6} alkylcarbonyl, C_{3-6} cycloalkylcarbonyl, carbamoyl, mono- or di-C_{1-4} alkyl-substituted carbamoyl, C_{1-6} alkylsulfonyl, C_{3-6} cycloalkylsulfonyl and a phenyl, naphthyl, phenoxy, benzoyl, phenoxycarbonyl, phenyl-C_{1-4} alkylcarbamoyl, phenylcarbamoyl, phenyl-C_{1-4} alkylcarbonylamino, benzoylamino, phenyl-C_{1-4} alkylsulfonyl, phenylsulfonyl, phenyl-C_{1-4} alkylsulfinyl, phenyl-C_{1-4} alkylsulfonylamino or phenylsulfonylamino which may be substituted by 1 to a 4 substituents selected from the group consisting of C_{1-4} alkyl, C_{1-4} alkoxy, halogen, hydroxy, benzyloxy, amino, mono- or di-C_{1-4} alkyl-substituted amino, nitro and C_{1-6} alkylcarbonyl, or ⑥ a C_{7-18} aralkyl, C_{8-18} arylalkenyl, C_{8-18} arylalkynyl or C_{3-7} cycloalkyl-C_{1-6} alkyl group which may be substituted by 1 to 5 substituents selected from the group consisting of a C_{1-4} alkyl, halogen, nitro, cyano, hydroxy, C_{1-4} alkoxy, C_{1-4} alkylthio, amino, mono- or di-C_{1-4} alkyl-substituted amino, cyclic amino, C_{1-4} alkylcarbonylamino, aminocarbonyloxy, mono- or di-C_{1-4} alkyl-substituted aminocarbonyloxy, C_{1-4} alkylsulfonylamino, C_{1-4} alkoxycarbonyl, hydroxycarbonyl, C_{1-6} alkylcarbonyl, C_{3-6} cycloalkylcarbonyl, carbamoyl, mono- or di-C_{1-4} alkyl-substituted carbamoyl, C_{1-6} alkylsulfonyl, C_{3-6} cycloalkylsulfonyl and a phenyl, naphthyl, phenoxy, benzoyl, phenoxycarbonyl, phenyl-C_{1-4} alkylcarbamoyl, phenylcarbamoyl, phenyl-C_{1-4} alkylcarbonylamino, benzoylamino, phenyl-C_{1-4} alkylsulfonyl, phenylsulfonyl, phenyl-C_{1-4} alkylsulfinyl, phenyl-C_{1-4} alkylsulfonylamino or phenylsulfonylamino which may be substituted by 1 to 4 substituents selected from the group consisting of C_{1-4} alkyl, C_{1-4} alkoxy, halogen, hydroxy, benzyloxy, amino, mono-or di-C_{1-4} alkyl-substituted amino, nitro and C_{1-6} alkylcarbonyl; and ring A is a benzene ring which may be substituted by 1 to 3 substituents selected from the group consisting of a C_{1-4} alkyl, halogen, nitro, cyano, hydroxy, C_{1-4} alkoxy, C_{1-4} alkylthio, amino, mono- or di-C_{1-4} alkyl-substituted amino, cyclic amino, C_{1-4} alkylcarbonylamino, aminocarbonyloxy, mono- or

di-C_{1-4} alkyl-substituted aminocarbonyloxy, C_{1-4} alkylsulfonylamino, C_{1-4} alkoxycarbonyl, hydroxycarbonyl, C_{1-6} alkylcarbonyl, C_{3-6} cycloalkylcarbonyl, carbamoyl, mono- or di-C_{1-4} alkyl-substituted carbamoyl, C_{1-6} alkylsulfonyl, C_{3-6} cycloalkylsulfonyl and a phenyl, naphthyl, phenoxy, benzoyl, phenoxycarbonyl, phenyl-C_{1-4} alkylcarbamoyl, phenylcarbamoyl, phenyl-C_{1-4} alkylcarbonylamino, benzoylamino, phenyl-C_{1-4} alkylsulfonyl, phenylsulfonyl, phenyl-C_{1-4} alkylsulfinyl, phenyl-C_{1-4} alkylsulfonylamino or phenylsulfonylamino which bay be substituted by 1 to 4 substituents selected from the group consisting of a C_{1-4} alkyl, C_{1-4} alkoxy, halogen, hydroxy, benzyloxy, amino, mono- or di-C_{1-4} alkyl-substituted amino, nitro and C_{1-6} alkylcarbonyl.

10. A compound as claimed in claim 1, wherein k is 0 to 2 and m is 1 to 5.

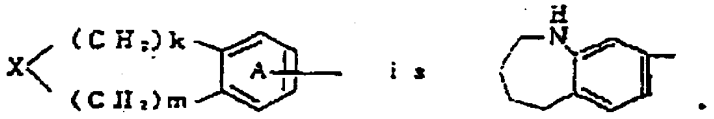
11. A compound as claimed in claim 1, wherein k is 0 and m is 2 to 5.

12. A compound as claimed in claim 1, wherein X is an oxygen atom or R^1-N< wherein R^1 is as defined in claim 1; k is 0 to 2; m is 2 to 5; n is 1 to 3 and R^2 is a hydrogen atom or a C_{7-10} aralkyl group which may be substituted by a C_{1-4} alkyl, halogen, nitro or C_{1-4} alkoxy.

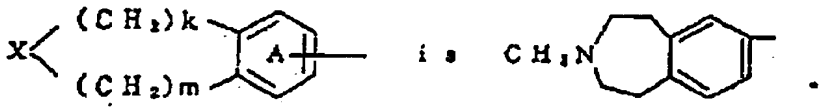
13. A compound as claimed in claim 12, wherein R^1 is a hydrogen atom, a straight-chain or branched C_{1-7} alkyl group, a C_{7-10} aralkyl group or a C_{2-6} alkylcarbonyl group.

14. A compound an claimed in claim 1, wherein n is 2 and R_2 is a benzyl group.

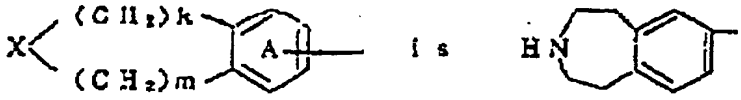
15. A compound as claimed in claim 1, wherein



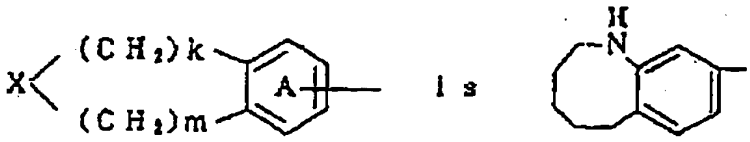
16. A compound as claimed in claim 1, wherein



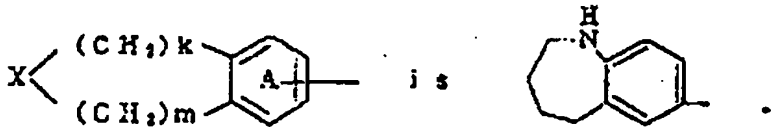
17. A compound as claimed in claim 1, wherein



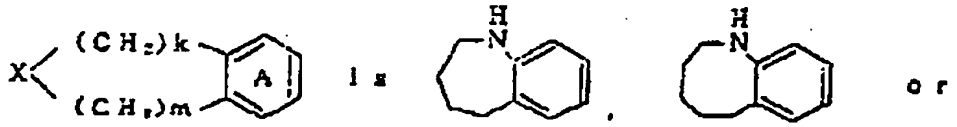
18. A compound as claimed in claim 1, wherein

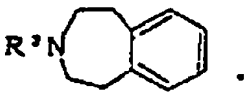


19. A compound as claimed in claim 1, wherein



20. A compound as claimed in claim 1, wherein





wherein R^3 is a hydrogen atom or a C_{1-3} alkyl group; n is 2 and R^2 is a benzyl group.

21. A compound as claimed in claim 1 selected from 8-[1-oxo-3-[1-(phenylmethyl)piperidin-4-yl]propyl]-2,3,4,5-tetrahydro-1H-1-benzazepine or a salt thereof;

3-methyl-7-[1-oxo-3-[1-(phenylmethyl)piperidin-4-yl]propyl]-2,3,4,5-tetrahydro-1H-3-benzazepine or a salt thereof;

7-[1-oxo-3-[1-(phenylmethyl)piperidin-4-yl]propyl]-2,3,4,5-tetrahydro-1H-3-benzazepine or a salt thereof;

9-[1-oxo-3-[1-(phenylmethyl)piperidin-4-yl]propyl]-1,2,3,-4,5,6,-hexahydro-1-benzazocine or a salt thereof;

7-[1-oxo-3-[1-phenylmethyl)piperidin-4-yl]propyl]-2,3,4,5-tetrahydro-1H-1-benzazepine or a salt thereof;

8-[1-oxo-3-[1-(phenylmethyl)piperidin-4-yl]propyl]-2,3,4,5-tetrahydro-1H-1-benzazepine fumarate;

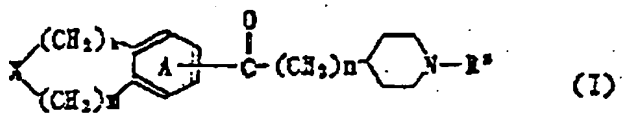
3-methyl-7-[1-oxo-3-[1-(phenylmethyl)piperidin-4-yl]propyl]-2,3,4,5-tetrahydro-1H-3-benzazepine dihydrochloride;

7-[1-oxo-3-[1-(phenylmethyl)piperidin-4-yl]propyl]-2,3,4,5-tetrahydro-1H-3-benzazepine fumarate;

9-[1-oxo-3-[1-(phenylmethyl)piperidin-4-yl]propyl]-1,2,3,4,5,6-hexahydro-1-benzazocine fumarate;

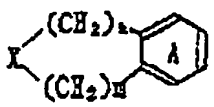
7-[1-oxo-3-[1-phenylmethyl)piperidin-4-yl]propyl]-2,3,4,5-tetrahydro-1H-1-benzazepine fumarate.

22. A process for producing a condensed heterocyclic compound of the formula (I):



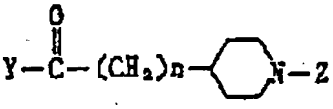
(I)

wherein X is an oxygen atom, a sulfur atom or R^1-N< wherein R^1 is a hydrogen atom, a hydrocarbon group which may be substituted or an acyl group which may be substituted; R^2 is a hydrogen atom or a hydrocarbon group which may be substituted; ring A is a benzene ring which may be substituted; k is a whole number of 0 to 3; m is a whole number of 1 to 8; and n is a whole number of 1 to 6, or a salt thereof, which comprises reacting a compound of the formula (III):



(III)

wherein each symbol is as defined above, or a salt thereof, with a compound of the formula (II):



(II)

wherein Y is a halogen; Z is an amino-protecting group; n is as defined above, or a salt thereof and removing the protective group, followed, if necessary, by

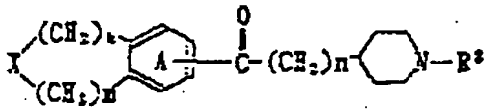
i) reacting the product compound wherein Z is a hydrogen atom with a compound of the formula $R^{2'}$-Y' wherein $R^{2'}$ is a hydrocarbon group which may be substituted; and Y' is a leaving group or

ii) reacting the product compound wherein X is H-N< with a compound of the formula $R^{1'}$-Y' wherein $R^{1'}$ is a hydrocarbon group which may be substituted or an acyl group which may be substituted; and Y' is as defined above.

23. A cholinesterase inhibitor which contains a condensed heterocyclic compound of the formula (I) as claimed in claim 1 or a salt thereof.

24. A pharmaceutical composition for an agent for senile dementia or/and Alzheimer's disease which contains an effective cholinesterase inhibiting amount of a compound of the formula (I) as claimed in claims 1 to 21 or a pharmaceutically acceptable salt thereof.

25. Use of a compound of the formula (I):



(I)

wherein X is an oxygen atom, a sulfur atom or R^1-N< wherein R^1 is a hydrogen atom, a hydrocarbon group which may be substituted or an acyl group which may be substituted; R^2 is a hydrogen atom or a hydrocarbon group which may be substituted; ring A is a benzene ring which may be substituted; k is a whole number of 0 to 3; m is a whole number of 1 to 8; and n is a whole number of 1 to 6, or a salt thereof as a component in the preparation of a cholinesterase inhibitor. 26. A compound as claimed in claim 1, wherein K is 0 to 2; m is 2 to 5; n is 1 to 3 and R^2 is a hydrogen atom or a C_{7-10} aralkyl group which may be substituted by a C_{1-4} alkyl, halogen, nitro or C_{1-4} alkoxy. 27. A compound as claimed in claim 26, wherein R^1 is a hydrogen atom, a straight-chain or branched C_{1-7} alkyl group, a C_{7-10} aralkyl group or a C_{2-8} alkylcarbonyl group.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 91 11 9818

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A	EP-A-0 296 560 (EISAI CO., LTD.) * example 23,170,171,175; claims *	1,23,24	C07D401/06 C07D405/06 C07D409/06
A	EP-A-0 288 563 (EISAI CO., LTD) * example 44, 63 ; claims *	1,24	A61K31/445
A	EP-A-0 351 282 (SYNTHELABO) * claims *	1,24	

TECHNICAL FIELDS SEARCHED (Int. Cl.5)

C07D

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	03 MARCH 1992	VAN BIJLEN H.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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A : technological background
O : non-written disclosure
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T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
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